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THE TOXINS AND VENOMS AND THEIR ANTIBODIES

BY

EM. POZZI-ESCOT

AUTHORIZED TRANSLATION

BY

ALFRED I. COHN, PHAR. D.

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INTRODUCTION.

Our knowledge of the toxins is of quite recent date. It is hardly twenty years since we began to acquire a knowledge of the facts that are detailed in this volume, and to which modern medicine owes its most recent and marvelous progress, particularly in serotherapy.

In this volume we have studied, besides the true toxins—substances of cellular origin and of albuminoid nature and unknown composition—other toxic substances, the nitrogenized alkaloidal bases introduced into science through the researches of Selmi, Armand Gautier, and von Behring, and which are highly hydrogenized nitrogenous crystallizable principles of definite chemical composition—the products of the more or less advanced breaking down of albuminoids.

Although these principles differ widely, by reason of their physiological properties as a whole, from the toxic albuminoids, or true toxins, it appears proper to consider them as products of

the advanced decomposition of these toxins—and in this respect their study becomes imperative, the more so as they are very frequently encountered together with the toxins, particularly in serpent-venoms, where their action is exerted in addition to that of the true toxins.

In the first volume of this collection we dwelt on the essentially reducing nature of the cellular functionation. To this functionation—causing the splitting up or decomposition by hydrolysis of nitrogenized albuminoid foods—is due the formation of these toxic basic products within the organism, whether normally, or because of certain pathological conditions.

This alone suffices to show that, during physiological life, oxygen plays an essentia ly antitoxic rôle within the organism.

It is hoped that this succinct résumé, which it has been sought to make as clear as possible, will be of service to those who, while not scientists actively engaged in scientific progress, desire to be abreast of the knowledge of modern evolution, but yet are not in a position to consult original papers or large treatises.

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TOXINS AND VENOMS.

PART I.

GENERALITIES REGARDING TOXINS AND ANTITOXINS.

CHAPTER I.

ALKALOIDAL TOXINS. PTOMAINES AND LEUCOMAINES.

Alkaloidal Products of Cellular Life.

Before entering upon the study of the true toxins, which are products of an alkaloidal nature and of unknown composition, it is necessary to say a few words regarding the most definite of the toxic alkaloidal principles that are frequently encountered under various conditions, conjointly with the true toxins, particularly in venoms, and which, furthermore, are closely allied to these albuminoid toxins.

These principles are formed in essentially reducing media, whether it be within the body of the organism, and by the simple exercise of its normal function, in which case the principles bear the generic name *leucomaines* *; or whether due to the action of anaerobic microbes, when they are designated as ptomaines.† These basic principles, which are essentially the products of cellular secretion, are usually toxic, and sometimes even extremely to.

As we shall presently see, ptomaines are essentially products formed during putrefactive fermentation. The toxic properties of extracts from the cadaveric fluids have long been known. Already in 1838 Panum ‡ had met with these products in snake venoms. Bergmann and Schmiedberg § in 1868 isolated from septic pus a toxic substance which they named *sepsin*; and almost at the same time Zuelzer and Sonnenschein ‖ reported having isolated from anatomical preparations an alkaloid possessing mydriatic properties. It is, however, due particularly to the researches of Selmi and

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* ARMAND GAUTIER: Sur les leucomaines, nouveaux alcaloides, dérivés de la transformation des substances protéiques des tissus vivants. *Bull. Soc. Chim.*, 2e série, XLIII, p. 158.

† ARMAND GAUTIER: "Communication sur les bases d'origine putréfactive." *Bull. Soc. Chim.* (2), XXXVII, p. 305.

‡ *Virchow Archiv.*, X, p. 301.

§ *Medic. Centralblatt*, 1868, p. 497.

‖ *Berlin. Klin. Woch.*, 1869, No. 2.

Armand Gautier that we are now so well informed regarding these toxic principles.

The labors of Armand Gautier were first published in his *Traité de Chimie Appliquée à la Physiologie*; those of Selmi in the *Actes de l'Académie de Bologne*.

At first sight, there appears to be a great difference between these alkaloidal bases, the ptomaines and leucomaines, and the albuminoid toxins proper. The toxic bases of the first two groups are quite definite chemical products which can be generally obtained quite pure, and frequently in crystalline form. The toxins proper, on the other hand, are highly complex albuminoid substances which greatly resemble the true diastases in all their properties.

Nevertheless, between the toxic alkaloids, ptomaines and leucomaines, and the toxic albuminoids, or more properly toxins, there exists no absolutely sharp line of demarcation, but there is a gradual passage from the one to the other by every intermediary grade, as a result of the breaking down of the albuminoid molecule.

We shall see, moreover, as we proceed, that these substances are formed under coexistent circumstances, and that they are, hence, found together, whether it be in virus or in snake venom.

We will first consider the ptomaines, and then the leucomaines.

Ptomaines.

This name is more specially reserved to designate those alkaloidal substances, generally highly hydrogenized, that are formed outside the organism, from the fermentative action of anaerobic microbes on albuminoid substances.

These bases are generally volatile, with an intense and tenacious purulent odor; often, however, they possess a floral odor (aubépine, syringa), and even like that of musk. They combine readily with acids and with the chlorides of the heavy metals, yielding crystallizable salts.

The ptomaines afford no specific reaction whereby they may be readily identified; and their identification is effected only after a painstaking analysis.

We must here call attention, however, to several of their more common properties, beginning with their basic character, their oxidizability by the air and consequently their well-defined reducing power —a property that led Selmi to propose a mixture of ferric chloride and potassium ferricyanide as a reagent for their detection.* They are precipitated by all the general reagents for the vegetable alkaloids. Selmi has given several reactions, such as those afforded by sulphuric, hydrochloric, and nitric acids, which appear, however, to apply much

* Sulle ptomaïne od alcaloïdi cadaverici. Bologne, CLXXXVII, p. 11.

more to the impurities present than to the bases themselves.

The physiological action of these bases varies greatly; in some the action is an extremely toxic one, as in the case of neurine and muscarine, which are true ptomaines; there are others, such as cadaverine and putrescine, which are quite innocuous. The physiological action of these bases, like that of the true toxins, is studied by making hypodermic injections of solutions of the bases in healthy animals, such as guinea-pigs, rabbits, and dogs.

In animals, the principal phenomena observed by Selmi to follow the injection of the substances are the following: At first dilatation of the pupil, then constriction; tetanic convulsions, soon followed by muscular relaxation, and retardation, rarely acceleration, of heart-beat; absolute loss of cutaneous sensibility; loss of muscular contractility; paralysis of the vasomotors; greatly retarded respiration; stupor, followed by death with the heart in systole.

It must be observed that in a number of cases where toxic researches had been made in the past, these bases had been mistaken for poisons which were believed to have been introduced into the organism with criminal intent. No one will ever know how many have fallen victims in the past to ignorance regarding the cellular mechanism!

The extraction of these bases is a tedious and

difficult operation. The materials must first be exhausted with water slightly acidulated; then, after precipitating the albuminoids by boiling and defecating by adding lead acetate, the liquid is evaporated to one-half its volume and dialyzed in a vacuum.*

Phosphomolybdate is then added to the dialyzed liquid, and the precipitate formed, which now contains all the bases, decomposed by boiling with lead acetate. After removing the excess of lead, there is thus obtained a limpid solution of all the alkaloidal bases in the form of acetates. These are separated by alcohol and by means of fractional precipitations with various metallic salts, depending upon the known properties of the bases.

In order to facilitate their study, the ptomaines have been grouped under two distinct classes, the one embracing the cadaveric or putrefactive ptomaines, of undetermined microbial origin, the other containing the ptomaines formed by microbes of known character. Each of these two groups is itself divided into subgroups, as shown in the following table:

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* ARMAND GAUTIER: *C. rend. de l'Académie des Sciences*, CXIV, p. 1256. *Ibid.*, XCVII, p. 264, and XCIV, p. 1600.

GROUP I.

CADAVERIC PTOMAINES OF UNDETERMINED MICROBIAL ORIGIN.

a. Amines.
b. Guanidines.
c. Oxamines (fatty or aromatic).
d. Amido Acids.
e. Carbopyridic Acids and analogues.
f. Undetermined Ptomaines.

GROUP II.

PTOMAINES OF KNOWN MICROBIAL ORIGIN.

a. Ptomaines extracted from microbial cells.
b. Ptomaines from pathological urines.

We will not here enter upon a detailed study of the bases belonging to each of these groups. This subject is a vast one, requiring for its treatment a volume devoted to it alone. We will here simply touch upon the principal properties of several of the bases of each of the subgroups named.

Bases of Group I.

a. **Amines.**—Among these we find nearly all the fatty amines, such as the methylamines and the cyclic alkaloids such as pyridine. They are formed particularly by the putrefaction of fish.

Certain of these bases are very toxic, for in-

stance trimethylene diamine, the collidines, and the parvolines.

b. **Guanidines.**—Among the products of ordinary putrefaction there has been found so far only methyl-guanidine, $C_2H_7N_3$. This is a highly toxic base of which 0.2 Gm. is fatal to a guinea-pig.

c. **Oxamines.**—Under this designation the following bases are comprised: 1. Neurine bases; 2. oxygenized aromatic bases; 3. bases of unknown constitution. Amongst them we find neurine and choline, which are toxic, and betaine, which is innocuous. They are found particularly in putrid fish.

d. **Amido Acids.**—These ptomaines, which are usually innocuous in small quantities, are particularly the products of the decomposition of albuminoid substances. Among them we find glycocoll, leucine, and tyrosine, as members of this group.

e. **Carbopyridic and Carboquinoleic Acids.**—So far only one base is known belonging to this group, and that is morrhuic acid, which is found in the decomposed livers of codfish, and which is a powerful appetizer and stimulant in disassimilation.

f. **Undetermined Ptomaines.**—Under this heading are classed certain undetermined bases, such as those found in normal urines, and in spoiled meats and bread.

Bases of Group II.

a. **Ptomaines Isolated from Cultures of Pathogenic Bacteria.**—Bacterial cultures contain, besides the true toxins, a certain number of alkaloidal bases which sometimes possess considerable toxicity.

In the cultures of streptococcus pyogenes there are found trimethylamine and xanthic bases; in those of staphylococcus pyogenes aureus are found xanthic bases and creatinine; while pyocyanine and pyoxanthine are found in the cultures of bacillus pyocyaneus, etc.

b. **Ptomaines Isolated from Pathological Urines.**—Toxic ptomaine bases have been found in the urines of a large number of diseases.* It is quite probable that these bases are the results of a general pathological condition due to some bacterial disease, the toxic products of which are eliminated by the kidneys.

From the urines of epileptics Griffiths † isolated a colorless base crystallizing in prisms having the formula $C_{12}H_{15}N_5O_7$, and which was found to be exceedingly toxic; the same investigator isolated from the urines of eczematous subjects a ptomaine

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* Griffiths: *C. rend. de l'Académie des Sciences*, cxv, pp. 285 and 667.

† E. Pouchet: Contribution à l'étude des matières extractives de l'urine, *Thèse*, Paris, 1880; *Ibid.*, *C. rend. de l'Académie des Sc.*, xcvii, p. 1560; Bouchard: *C. rend. Soc. de Biolog.*, Aug. 12, 1882.

which he named *eczemine*,* and which is also highly toxic.

In certain cases of cystinuria there are found in the urine sulphurized ptomaines, and in measles the urine contains an undetermined ptomaine, *rubedine*, which is very poisonous. *Typhotoxine*, a very toxic ptomaine, has been isolated from the urine of typhoid patients; *erysipeline*, a hardly less toxic base, exists in the urine of erysipelatic subjects; while *spasmotoxine*, *tetanotoxine*, and *tetanine*, exceedingly active alkaloids, are found in the urines of tetanus patients.†

As a general rule, all abnormal urines contain toxic bases; the kidneys appear, in fact, to serve as a means of eliminating the toxic products that form in large quantity whenever, and for whatever cause, the organism ceases to functionate normally, whether it be as a whole, or in any one of its parts.‡

Leucomaines.§

The leucomaines are basic substances, nearly allied to the ptomaines, but still more closely related to the ureides. They are formed directly

* GRIFFITHS: *C. rend. de l'Académie des Sciences*, CXVI, p. 1206.

† BRIEGER: Untersuchungen über die Ptomaine, dritten Teil, p. 93; *Berichte d. D. Chem. Gesellschaft*, 1886, p. 3159; 1887, p. 69.

‡ CHARRIN: *Les poisons de l'urine*: Encyclopédie Léauté.

§ ARMAND GAUTIER: *Bull. Acad. de Médecin* (2), XV, p. 115.

or indirectly by the breaking down of protoplasmal albuminoids. The agents that effect the breaking down are the hydrolyzing ferments of the economy. It is well to recall here that these phenomena of hydrolyzation occur within the cell itself and in a practically reducing medium, as we have already stated. The inmost mechanism of these phenomena cannot here be detailed; it will be found described by Armand Gautier in the *Chimie Biologique*, and in his work *Chimie de la Cellule Vivante*.*

The extraction of these bases is an extremely delicate operation. It is necessary to operate with a large quantity of substance, say 50 kilos. The substance is finely chopped, then exhausted with twice its weight of water acidulated with acetic acid (0.2 Cc. per liter) and containing a trace of oil of mustard, which is intended to act as an antiseptic. The albuminoids are precipitated by boiling, the solution then filtered, evaporated in a vacuum at 60° C., and the bases extracted with 95-per cent. alcohol.

The alkaloidal bases obtained in this manner are separated by crystallization from alcohol or by various other chemical methods, the description of which we will not enter upon here.

In order to facilitate the study of the leuco-

* ARMAND GAUTIER: Leçons de chimie biologique. Published by Masson; *Ibid.*, Chimie de la cellule vivante. Also published by Masson.

maines they are classed under three groups, according to their chemical affinities. These groups are as follows:

1. **Xanthic Leucomaines.** — The bases of this group appear to have a composition resembling that of uric acid. When hydrolyzed, they yield urea and guanidine. They are weak bases, and exhibit both basic and weakly acid properties. They all possess the common characteristic of being precipitated by copper acetate in acid solution with heat, and by ammoniacal silver nitrate in the cold.

According to Kossel, these bases are derived from the nucleo-albumins which are found in the cell nuclei, and which are, as we know, substances rich in nitrogen and phosphorus.

Among the bases of this group may be mentioned *adenine*, $C_5H_5N_5$, which is obtained from infusions of tea.* This base is non-toxic; it was discovered by Kossel,† and it crystallizes easily.

Some others of this group are:

Guanine, $C_5H_5N_5O$, non-toxic, discovered by Unger; *pseudo-xanthine*, obtained from muscular tissues; *sarcine*, $C_5H_4N_4O$, also but slightly toxic, discovered by Scherer; *xanthine*, $C_5H_4N_4O_2$, which is found in many urines, and which acts as a stimulant on the cardiac muscles; *paraxanthine*,

* KRUGER: *Bull. Soc. Chim.* (3), VIII, p. 687.

† KOSSEL: *Zeitschrift für physiol. Chim.*, X, p. 248; and *Bull. Soc. Chim.* (3), III, p. 239.

$C_7H_8N_4O_2$, a toxic base found in certain pathological urines; *caffeine* and *theobromine*, powerful diuretic bases; and *carnine*, $C_7H_8N_4O_3$, from meat, a muscular stimulant like caffeine.

2. **Creatinic Leucomaines.**—These have for their type guanidine; they differ from the xanthic bases in that they are not precipitated by copper acetate, but frequently are by ammoniacal silver nitrate. They yield double salts with the chlorides of zinc and cadmium. To this group belong *glycocyanine*, $C_3H_7N_3O_2$, and *glycocyanidine*, $C_3H_7N_3O$, both very toxic; *creatine*, $C_4H_9N_3O_2$, only slightly toxic; *creatinine*, $C_4H_7N_3O$; *lysatine*, which very easily decomposes to form urea; *lysatinine*, *xanthocreatine*; *arginine*, a vegetable base, etc.

3. **Neurinic Leucomaines.**—These have none of the characteristics of the preceding bases; their type is neurine, a highly toxic base found in the brain, nerves, and certain fish ova. These bases are sometimes normally produced by the animal economy, and are also frequently the result of microbic action. They are the result of the simple phenomena of fermentative hydrolyzation of protagons and lecithins. Among these bases are *choline*, a weak alkaloid, and *betaine*, which appears to be non-toxic.

The former has the formula $C_5H_{15}NO_2$; it was discovered by Stocker. Wurtz synthesized it by combining trimethylamine and glycol-monochlor-

hydrine, and treating the resulting hydrochloride with silver oxide. Betaine, $C_5H_{11}NO_2$, is found in beets; it was discovered by Scheibler. Neurine is, chemically, trimethylvinylammonium hydrate.

4. **Undetermined Leucomaines.** — Among these bases several are important in more than one respect. For instance *spermine*, which is found in the sperm, is a strong base possessing a powerfully dynamic and tonic action on the nerves. It acts as an oxidizer. Spermine was first obtained by Schreiner * from the sperm of mammifers in which it occurs as a phosphate. It has the formula $C_5H_{14}N_2$. It was physiologically studied by Poehl, Tarchanoff, Weljaminoff, and Joffroy.† *Plasmaine*, a toxic base found in the blood and discovered by R. Wurtz,‡ has the formula $C_5H_{15}N_5$; *protamine*, from fish milt, was discovered by Micocher.§

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* *Liebig's Ann. der Chemie*, CXCIV, p. 68.

† *Journ. Soc. Phys. Chim. Russe*, 1893, No. 2; and *Bull. Soc. Chim.* (3), XII, p. 243.

‡ *Leucomaines du Sang Normal*, Thèse, Paris, 1889.

§ *Joh reab. de Thiérchen*, 1874, p. 341; Picard, *Ibid.*, p. 355.

CHAPTER II.

TOXINS AND ANTITOXINS.

We have already seen, in the preceding chapter, that the microbes and the cells of various organisms are capable of secreting definite products of a toxic nature to which the names "ptomaines" and "leucomaines" have been given. Researches, which were begun scarcely twenty years ago, have shown that, besides these crystallizable and definite products, we meet with basic non-crystallizable substances of unknown composition, possessing special toxic properties, sometimes even of extreme violence. These substances have been named "toxins."

At first this generic name was extended toward indefinite basic organic products that could be isolated from tissues and tumors both normal and abnormal; later on, however, the name was applied to toxic substances, equally indefinite, isolated from the culture media of microbes and the active constituent of various venoms.

It is only since 1885, when Charrin called attention to them, that investigations began to be

made regarding them. In 1888 Roux and Yersin,* in their beautiful researches on diphtheria, pointed out the diastatic nature of the properties of the active albuminoid matter existing in the cultures of the specific bacilli of this disease. From that period, these products began to take a more and more prominent place, from year to year, in the study of pathological affections, and, by developing the knowledge of immunity, they have opened a new path to the investigations of therapeutic technic.

It is due to the knowledge of these principles that we have learned that the infectious microbes, far from acting as they were believed to do only a few years ago, and which Pasteur strongly maintained to be by vital parasitism—such as would be the case with the carbonizing bacteria which, according to Pasteur, act by diverting the oxygen, or causing capillary embolisms—owe their pathogenic action to the toxic substances which are the products of their secretion, and which spread throughout the organism, even though the microbe frequently is localized in a very circumscribed spot, as in tetanus and in diphtheria.

The idea of intoxication by these products has now replaced the idea of the direct action of the

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* Roux and Yersin: Mémoire sur Diphtérie. *Ann. Inst. Pasteur*, 1888–1889.

microbe on the elements or the liquids of the organism.

The occurrence that takes place in diphtheria and tetanus is one of the best examples to cite in support of this view.

Here, in fact, the pathogenic microbe is found only in a very limited area in the organism attacked —the false membrane, in the case of diphtheria, or frequently only a slight wound in the case of tetanus, and the microbe becomes localized there only. Now, in both cases, there are general phenomena of toxic effects. There must hence be a diffusion of toxic substances which, distributed by the blood, affect the different systems and exert a toxic action on the entire organism.

It must be observed that the toxins act as toxic agents only when in a condition to be introduced into the circulation subcutaneously. The cause of this innocuousness of the toxins when given per os has frequently been studied. It appears to be quite probable that the cause of the attenuation of the morbid properties is due to the interveniton of the digestive microbes. Such is the opinion of Levaditi and Charrin *; it is also the conclusion that is to be drawn from the experiments of Mme. Metchnikoff and of Cal-

* Charrin and Levaditi: Le sort de toxines introduites dans le tube digestif. *Journal de Physiologie et de Pathologie Générales*, 1898, p. 226.

mette * on the modifications undergone by a vegetable toxalbumin, abrin, and by serpent venoms, when these toxalbumins are inoculated with the bacillus subtilis chromogenus. Moreover, Charrin and Lefèvre,† on the one hand, and Nencki, Sieber and Somanowsky,‡ and Carrière,§ on the other hand, have discovered that the digestive ferments, particularly trypsin, destroy, even though but little, the toxins secreted by the Loeffler and Nicolaier bacilli. This is practically contrary to the opinion of Behring and of Rauson,‖ according to which the innocuousness of the microbial poisons when administered per os is due exclusively to the lack of absorption.

Nature of the Toxins.—The molecules of the toxins are very nearly like those of the diastases. Like these, the toxins appear to have a very complex, and very unstable, internal structure. Their mode of action frequently depends, as in the case of the diastases, upon the medium in which they occur. Again, like the diastases, they are generally destroyed by the action of sufficiently prolonged heat, but less easily, for there are certain toxins that resist a temperature of 100° C. for an indefinite period. They are, like the diastatic albuminoids,

* Citing Metchnikoff.
† *C. rend. de la Soc. de Biologie*, 1898.
‡ *Centralblatt für Bakt.*, 1898.
§ *C. rend. de la Soc. de Biologie*, 1899.
‖ *Deutsche Med. Wochenschr.*, 1898, No. 8.

insoluble in strong alcohol, and are precipitated from their solutions on the addition of this reagent. They easily adhere to precipitates that form in liquids in which they occur in solution, and possess the remarkable property of diastases in that imponderable masses produce considerable results.*

Although closely allied to certain alkaloidal bases, the toxins are sharply distinguished by the remarkable fact that their action is never immediate, but is always preceded by a period of incubation, which may be quite long.

Like the alkaloidal bases, they appear to result from the hydrolyzing breaking down of albuminoids and nucleo-albumins, and they appear to be intermediary, from a chemical point of view, between these bodies, the general characters of which they retain, and the alkaloids proper, or ptomaines, to which we have called attention, and the principal chemical and physiological properties of which they possess.

No absolutely precise knowledge is had regarding the chemical nature and constitution of these remarkable substances. A number of analyses of these substances have been published which, in general, permit no definite conclusion to be drawn.†

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* See Pozzi-Escot: Les diastases et leurs applications, published by Masson, 1900; and *Traité de Physico-chimie.*

† Regarding this see the works by Koch and Brieger, *Deutsche Medicin. Wochenschr.*, Oct. 22, 1891.

I have, however, elaborated several speculative ideas regarding this subject.*

We must here call particular attention to the ideas of Ehrlich regarding the constitution of the toxins. According to this scientist, their molecules contain two functional groups; the one, to which he has given the name "haptophore," is that which enables the toxin to attach itself to any cellular element whatever, and which it then renders non-toxic by means of the other, or "toxophore," group. We will particularize farther on regarding this very important conception.

Origin of the Toxins.—These toxic bodies result either as the products of the secretion of microbial life, or as the result of the normal functionation of cellular life in the higher vegetable or animal organisms.

They are the direct products of life, and do not result, as was formerly believed, from a more or less profound modification of the more or less complex albuminoids that serve as a food for the various species of microbes, or for the cellular elements.

The vegetable toxins are less numerous than

* Pozzi-Escot: Nature des Diastases. Published by J. Rousset, Paris, 1903. See also Recherches de la Nature Chimique des Diastases Oxydantes. *Revue génér. de chimie*, VII, pp. 129–136; and Aperçus sur la nature chimique des Diastases, *Bulletin de l'Association de Chimistes*, 1904, p. 769.—Propriétés Catalytiques de Quelques Diastases; *Ibid.*, 1904, p. 1247.

the animal toxins. They are met with, nevertheless, in almost all mushrooms which are reputed or known to be toxic; the seed of the castor plant contains a very toxic vegetable albuminoid, as is likewise the case with Abrus precatorius (jequirity-bean), and certain others.

The true physiological toxins occupy a very important place in the realization of the conditions that govern health, sickness, and death.

We will see later on that they are met with in quite large number in the bladder, whence they are voided in the urine. Their number varies considerably, according to diverse influences (waking, slumber, eating, fasting, fatigue, oxygen, brain-work, health, disease, etc.). It is necessary here to observe that the renal system serves for the purification of the entire organism, and that in the case of normal life we will find in the renal system a large portion of the products of the cellular secretion of the organism, and among the number there are found, as we know, a certain number of alkaloidal bases. We will take up later the subject of urinary toxicity.

Autointoxications.—The toxins are also encountered, and often in some number, in the muscular tissues and in the blood, particularly in those of batrachians, mureids, and saurians. In the organism these toxins, developed by the activity of the various cells, may cause autointoxication

whenever, for one cause or another, their normal elimination ceases. "Although there are an infinity of diseases," remarked Prof. Bouchard, "there are but a few ways of becoming ill." Of these ways that of autointoxication is the most frequent. "What else is it, then," says Prof. Charrin, "in the last analysis, but to die from affections of the kidney, the liver, the heart, the lung, etc., if it be not to succumb because of the lack of oxygen, the accumulation of carbonic acid, the influence of the numerous urinary poisons, the action of acids, of salts, of biliary pigments, or the effect of noxious principles, which the hepatic cell must normally destroy or at least attenuate."

These autointoxications, always due to poor elimination of toxic principles, toxins formed in very great number in the organism, and which the normal modes of evacuation or destruction do not eliminate, are always found to be the cause of all diseases, even those that are manifested by attacks of the cerebro-spinal axis, and that exhibit variously mania, insanity, symptoms of hyperexcitability, etc.

These autointoxications are controlled by the nervous system, and the latter alone is the cause of a larger number of maladies than is generally believed; in fact, if the mechanism of nutrition be reduced to its most simple elements, it will be seen to consist of the penetration of the foods, of

the plasmatic principles, to the cells; of their transformation within the interior of the cells, and finally the rejection of all the matter that could not be utilized. It is the nervous system that commands or dominates this mechanism, that controls the taking-up of assimilable elements and the elimination of toxic principles, the fruit of assimilation or disassimilation, and in such a manner, in fact, that this same nervous system can, at its will, cause starvation, or intoxicate.

The marvelous cures obtained by magnetic methods are due to no other causes than favorable changes in the nervous system.

General Mode of Action.—The toxins, of whatever kind, always behave like diastases, in the sense that their definite action appears to be absolutely independent of their mass, and that imponderable quantities suffice to cause serious morbid affections and profound modifications in nutrition.

Koch has shown that tuberculin is capable of affecting 60 trillion times its weight of the living human being. According to Vaillard one milligramme of tetanus toxin will kill a horse weighing 600 kilos. These two examples show what an enormous power the toxins possess.

My views regarding the manner in which diastases act I have developed at length in my work *Nature des Diastases.* The close analogy between these substances and the toxins, an analogy upon

which, moreover, I have dwelt at some length, permits me to refer the reader who is desirous of fuller details to the small work just mentioned.

The mode of action of diastases resembles singularly closely that of the catalytic substances, and we will admit, for the moment, that they act by intermediary combination, resulting in their rapid decomposition.

We owe to Ehrlich * a new conception relative to the nature and mode of action of the diastases, and which to-day plays an important rôle in all our conceptions regarding immunity.†

According to this scientist, the complex molecule of albuminoid substances is constituted by a fixed central nucleus, and by a number of lateral chains or receptors, fixed to this nucleus, which possess diverse accessory functions, and which serve, particularly, for the nutrition of the cells. These receptors have a great affinity for the various substances necessary for the support of the living elements, and they seize upon the alimentary substances, in normal life, just as a leaf of the *Dionœa* seizes a fly which serves as its food.

In these special conditions the receptors may

* EHRLICH: *Klinisches Jahrbuch*, 1897, VI. *Proceedings of the Royal Society*, 1900, No. 482, p. 424. *Nothnagles' specielle Pathologie und Therapie*, 1901, VIII, Schlussbetrachtungen, p. 163.

† To have a complete exposé regarding this question, it will be profitable to consult No. 4 of this collection on *Sérums Immunisants*.

attach themselves to the complex molecules of albuminoid substances, such as the different toxins.

Ehrlich supposes, as we have already seen, that a toxin contains two special groups—a *toxophore* group, which poisons, and a *haptophore* group, which combines with the receptor. According to this theory, the toxophore group of a toxin can act on an organism *only* when the haptophore group of the toxin encounters a suitable attachment or receptor.

The receptors attached to the living protoplasmic molecule attract the toxin, just as a lightning-rod attracts the lightning.

It is hence clearly proved that the toxigenic poisons exert their noxious action on the cellular elements of sensitive organisms, by entering into combination with these.

Experience has shown that they attach themselves, in a most rigorously elective manner, to the tissues, and rapidly disappear from the general circulation. Numerous facts, clearly established, attest the reality of this fixation or attachment.

It is thus that von Behring and Wernicke * sought to ascertain the quantity of antitoxin (we will see farther on that this name is given to those substances which neutralize the activity of toxins

* Von Behring and Wernicke: Zeitschrift für Hygiene, XII.

under certain conditions) which, introduced a certain time after the introduction of the poison, will save the life of the animal. They have experimented with diphtheria toxin, which we will study later, and they have demonstrated that, if the antitoxic serum be introduced immediately after the toxin, a dose of antitoxin twice as large as that of the toxin suffices to effect a cure.

Eight hours after the administration of the toxin the dose must be trebled, while after thirty-six hours it is necessary to have recourse to a quantity of antitoxin eight times as great. These experiments show that the curative action of the antitoxin is so much the less the longer the period of time that has elapsed between the introduction of the toxin and the antitoxin. This is because the toxin has become so intimately attached to the tissues that the antitoxin introduced has not the power to destroy the combination. These facts have been confirmed by Donitz * and by the classic experiments of Decroly and Rousse.†

This is not, however, the case with cold-blooded animals, which, generally, are not affected by injections of poisonous toxins. Thus Metchnikoff ‡ and

* Donitz: Ueber die Grenzen der Wirksamkeit des Diphtheria Heilserums. *Deutsche Med. Woch.*, No. 27, 1897.

† Decroly et Rousse: *Arch. Int. de Pharmacodyn.*, III and VI; Masoin: *Arch. Intern. de Pharmacodyn.*, II, 1903.

‡ Metchnikoff: *L'Immunité*, Paris, 1902; Morgenroth: Zur Kenntniss des Tetanus des Frosches. *Deutsche Med. Woch.*, No. 35, 1898.

his pupils have been able to show that the toxins introduced into certain cold-blooded animals (Oryctes nasicorius) may remain for several months without alteration in their circulation.

If we consider the facts of the theory of Ehrlich's lateral chains, which we have mentioned, we are led to well-defined conclusions regarding the mode of action of the toxins. In fact, since these toxins exhibit a pronounced chemical affinity for the tissues, and while, on the other hand, they can attach themselves only because of the presence of certain functional groups of the protoplasmic molecules, this union can take place only in certain specific centers. This has been fully confirmed by experiments *in vitro*.

It is known, since the researches of Ehrlich,* Wassermann and Takaki,† Marie,‡ Metchnikoff,§ and a host of other scientists, that this fixation is due to a clearly elective property. It is for this reason that the tetanus toxin fixes itself only upon the nervous tissue, and that in this action all passes as if the nervous tissue had been provided with

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* Ehrlich: *Berl. Klin. Woch.*, No. 12, 1898.

† Wassermann and Takaki: *Berl. Klin. Woch., Med.*, p. 5, 1898.

‡ Marie: Sur les Propriétés Antitoxiques aux Centres Nerveux de l'Animal Sain. *Ann. Inst. Past.*, 1898, p. 1.

§ Metchnikoff: Recherches sur l'Influence de l'Organism sur les Toxines. *Ann. Inst. Past.*, 1899, p. 82.

functional groups possessing an elective affinity for the tetanic poison.

Means of Defense Possessed by the Organism against the Action of Toxins.—We have already seen that the renal organs serve for the elimination of the toxins normally produced in the organism by the simple play of its cellular mechanism. Experience has shown that the toxins introduced from without into the circulation are generally finally eliminated, even though in the meantime the modifications they have imprinted on the economy may be transmitted hereditarily; and that their influence on the general nutrition and the normal functionation of the entire organism persists even after their elimination.

Much has been said regarding the elimination of these toxins by the urine, but the experiments made by Métin, at the Institut Pasteur, have shown the inaccuracy of this assumption, and it has been necessary to seek another.

It has been remarked that oxidation destroys the toxins *in vitro*, and it has been thought that a process resembling disinfection may well take place within the tissues of the animal economy, but no decision has been arrived at regarding the possible mechanism of this action, which some attribute to the action of the oxidizing ferments of the organism, or to the action of certain special cells.

According to Pochl, there is developed as destroyer a substance possessing energetic oxidizing properties, which he has isolated and named *spermine*, and which is found in most of the organic fluids and particularly in the leucocytes, the special rôle of which we will presently study.

There develops still another cause of elimination, or, to be more exact, of the neutralization of the toxic principles in defense of the organism against the toxins, and that is the formation of *antitoxins*.

It is well known that the term *virus* has been reserved to designate physiological liquids which were characterized, when first they were known, by their property of transmitting to an organism certain functional affections, but the true character of which is to expend their toxicity upon the microbes which occur and are reproduced in the organism, or upon the organized plastidulary granulations, as in the case of the rabic virus, the special microbe of which has not as yet been isolated.

Pasteur, when studying rabies, found that the brain and spinal marrow of rabid animals contained the pure rabic virus in considerable quantity, and that every particle of the marrow was capable of imparting rabies to a perfectly healthy dog. After having ascertained this fact, he found that he could *attenuate the action of the virus*, either by passing the virus through certain animal organisms, such

as the monkey or rabbit, by gently heating, or even by allowing it to oxidize and partially dry in the air, or else by submitting it to the action of antiseptics or alternating electric currents of very high tension.

Experiments have shown that a deadly virus, attenuated by one of the means mentioned, may be injected, without danger of death, into the living animal; and what is still better, the animal thus treated acquires the power of resisting large doses of the virus, less and less attenuated, and that it is possible to reach a point where the animal economy may become habituated to very large doses of a highly virulent virus without the organism experiencing any visible illness—that is, the organism has been *vaccinated* with regard to the particular virus.

Experiments have shown that this property is not peculiar to microbial virus alone, but that it is common to the venoms the toxicity of which is essentially due to some toxins, with the exception of those agents noted.

The attenuated viruses act, as vaccins, through their soluble constituents, which, either directly, by modifying the nutrition of certain cells, or indirectly, by inducing reactions of the nervous centers which preside over this nutrition, profoundly change the conditions of life and give rise to the pathological condition—the vaccined state.

Experiments by Behring and Kitasato* have shown that the tumors of a vaccinated animal, freed from all organized matter visible under the microscope by filtration through porcelain, contains principles capable of directly or indirectly protecting other animals from the disease caused by the corresponding virus. Meanwhile, experiments have shown that the vaccinating matters are totally eliminated; nevertheless, after their elimination, the immunity acquired remains with the animal, which then continues to be protected against the corresponding virus.

Interest in this subject has incited numerous researches with a regard to bringing to light the mechanism of this immunization; and this will form the subject of another volume of this collection. We may state here, however, that there have been recognized two concurrent causes of this preservative action; the one, called *phagocytosis*, results from the fact that the microbe introduced into the vaccined organism becomes incapable of producing its usual toxins, while on the other hand the immunization renders the organism capable of secreting substances possessing an activity contrary to that of the virus, in fact true counter-poisons, comprised under the general name *antitoxins*.

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* *Deutsche Med. Wochenschr.*, 1890, p. 1113.

Phagocytosis.—We have seen that an organism subjected to a toxic invasion tends to protect itself by proper means of defense; and one of those is the direct putting into activity of the living cellular elements themselves, and in particular, the leucocytes, or white corpuscles, found in more or less number, according to pathological conditions, in the blood and lymphatic fluids.*

Metchnikoff has shown that the moment a foreign element, particularly a microbe, enters the organism, these leucocytes come flocking from all parts of the body, collect around the bacterial element, penetrate it, and begin to digest it. These elements have received the name *phagocytes*. The name *chemotaxis* has been given to the property by virtue of which they approach (positive chemotaxis) or move away from (negative chemotaxis) certain substances which affect them powerfully.

Experiments have shown that the leucocytes are attracted by the products secreted by pathogenic microbes, or saprophytes. Attracted by the latter, the white corpuscles surround, envelop, and finally digest them; and when it happens that all the pathogenic microbes within an organism

* It is necessary here to consult the work by LEVADITI: Le Leucocyte et ses Granulations. *Scientia*, Naud, publisher, Paris, 1903; also METCHNIKOFF: L'Immunité, Paris, 1902, Masson, publisher.

are absorbed, the organism survives, while in the contrary case it succumbs.

Attention must be called to this attack by the white corpuscles within the limits where they are normally confined. It is a pathologic diapedesis—a leucocytosis provoked by the irritation of the tissues—and caused either by the presence alone of foreign elements, or by the soluble products secreted by them.

When, for any reason whatever, this phagocytic action is impeded, the resistance of the organism to pathogenic infection ceases to be effective, and the organism may therefore be invaded by the microbe. Numerous causes may contribute to impede this action.

The Antitoxins.

We have seen that the second means of defense possessed by the organism resides in the action of special products, true defensive secretions, possessing an activity contrary to that of the toxins, and which are secreted by the cells of the organism under the influence of the vaccins.

This is a property common to every organism, and which is observed even in non-vaccinated subjects, although in this case the secretion forms with great difficulty and in small quantity.

When an organism subjected to the toxic action of a bacterial infection does not succumb to the

intoxication, it emerges from the test gifted with a new property, which may be augmented by habituation, and which borders on immunity.

At first we were content to vaccinate small animals in the laboratory, but in proportion as the discoveries in this domain extended, and there developed a need for large quantities of antitoxins, recourse was had to the larger animals, particularly horses and cattle. From the moment that large quantities of blood and antitoxic serum were at command, search was made for a means of isolating the antitoxin and determining its properties.

Experiments so far made have shown that the antitoxins are substances of an albuminoid nature, of unknown composition, and which are very closely united to the albuminoid substances of the serum. It must be observed, however, that Behring and Knorr oppose the assertion regarding the albuminoid nature of tetanic antitoxin, but their reasons for this do not appear to be well founded.

In general, these antitoxins are precipitable with the globulins, and possess quite considerable powers of resistance towards physical and chemical agents. Thus they are destroyed only at a temperature above 60–65° C. Kept in the dry state, in the residue of evaporated serum, and away from the light and all oxidizing action, it is possible to preserve their activity for a very long time.

They are essentially humoral substances; they

are found in the blood of vaccinated animals, from which may be obtained antitoxic serums with a specific but transient immunity; and they are also found in the plasmas of the lymph and exudates, in aqueous tumors, and in the milk. They are seldom found in the cells.

Mode of Action.—Frequent attention has been paid to the mode of action of the antitoxins upon the toxins, a phenomenon of great importance in relation to the phenomenon of immunity acquired against the toxins. At the beginning of our knowledge on this subject, the idea of a destruction of the toxin immediately suggested itself, and was advanced by von Behring.* According to this scientist the antibody inhibits the morbigenic action of the toxin by neutralizing the toxin, combining with the latter to form a compound of a chemical nature which is devoid of toxicity and without action on the organism. According to this theory, the influence of the antitoxin on the toxin is direct, and does not require the intervention of the living cellular protoplasm. Such was also the belief of Prof. Ehrlich.†

Buchner, a little later, believed that the antitoxin, instead of acting directly on the toxin, exercised a direct influence on the living elements

* Von Behring and Kitasato: *Deutsch. med. Wochenschr.*, 1890, p. 1113.

† Ehrlich: *Klin. Jahrb.* 1897, VI, p. 292.

of the organism, preserving them from intoxication.*

Such was also the opinion of Roux†; and Calmette demonstrated that a mixture of venom and of a non-toxic antivenom recovered its toxicity on being heated to 68° C., whereby the antivenom was destroyed (Calmette: *Le Venin des Serpents*, Paris, 1897, p. 58); and Wassermann arrived at the same result.‡

The array of proofs offered by these scientists, which we cannot here enlarge upon without uselessly extending our subject, would tend to make one believe, at first glance, that the antitoxin does not act directly on the toxin, but at the present time Buchner's theory appears untenable. Numerous researches have proved conclusively that the toxin and the antitoxin have a specific affinity for each other, by virtue of which these principles combine to form a substance free from all toxicity, but unstable, and which may be decomposed by heat or certain other factors.§

Some recent experiments by J. Martin and Cherry (*Proceedings of the Royal Society*, 1898, LXIII, p. 423) have clearly brought out this fact. These authors made mixtures of serpent venom with its

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* BUCHNER: *Münchener med. Wochenschr.*, 1893, p. 480.
† ROUX: *Annales de l'Institut Pasteur*, 1894, VIII, p. 724.
‡ WASSERMANN: *Zeitschr. für Hygiene.*
§ J. DANZSY: *Annales de l'Institut Pasteur*, XVI, p. 331.

antivenom, which they filtered through a layer of gelatin, under the supposition that, if the venom and its antivenom were not chemically combined, the former alone would be able to pass through into the filtrate, because its molecules are so much smaller. Martin and Cherry allowed the venom and its antivenom to remain in contact for varying periods before filtering. As the result of a series of experiments carried out with this idea, they have demonstrated that the filtrate obtained after allowing a few minutes' contact between the two substances, was decidedly toxic, while that obtained after a contact of half an hour was absolutely non-toxic. From this the authors conclude that the antitoxin enters into chemical union with the venom, but that the combination does not take place immediately, and requires a certain length of time for its accomplishment.

Ehrlich and Knorr have demonstrated that the neutralization is less rapid in dilute solutions than in concentrated ones.

Prof. Svante Arrhenius has completed our knowledge regarding the mode of combination between the toxins and the antitoxins, by demonstrating the occurrence of limited reactions analogous to the etherification of an alcohol by an acid, and in such a manner that there always exists, in a mixture of these two substances, a certain quantity of free toxin and antitoxin. This is an important

modification of the general ideas held in this respect.*

It appears necessary to bring here more clearly in evidence the fact that *the antitoxin inhibits the noxious action of the toxin, even outside the living organism, by uniting with it to form a compound in identically the same manner as when a strong base and a strong acid are brought together.* As we have seen, all the conditions of environment that favor or retard the formation of salts, in a like sense influence the neutralization of the toxin by its antitoxin.

Formation of Antitoxins.—Ehrlich's theory of side chains, to which reference has already been made, furnishes us with an explanation of the formation of the antitoxins in tumors. Let us suppose that, in the organism, a cell had come into contact only with certain toxic molecules incapable of compromising its life, and that the only result was the immobilization of the receptors which are united with the haptophore groups of the opposing toxins. It is known that, by virtue of a property inherent in all living organisms, during the phenomena of reparation, there is generally an overproduction of the neoformed

* SVANTE ARRHENIUS: La Physico-chimie des Toxines et des Antitoxines. *Conférences de la Société chimique de Paris*, May 20, 1904. See also MADSEN AND ARRHENIUS: Testkrift red indivulsen of Stotens Serum Institut. Copenhagen, 1902.

parts. In the case we here speak of, as the receptors fill an important function in the nutrition of the opposing cellular elements, once they become united with the toxic haptophores, they become incapable of filling their normal function of nutrition. Under these conditions the cells develop so large a quantity of receptors that, filling the cells, and not finding any more room, they spread into the blood and other liquids of the organism.

Under these conditions, every new injection of toxin into the organism is absorbed into the blood where it meets with the free receptors which possess great avidity for the haptophore group of its molecule, and the two groups immediately unite, before the haptophore group of the toxin has been able to attack and intoxicate a cellular element.

We thus see that the receptors which, when in a free state in tumors, play the rôle of antitoxics or antitoxins, become, within the cellular elements themselves, the vehicle of intoxications. Figuratively speaking, so long as these fixators are attached to the molecule of the living protoplasm they attract the toxin.

According to this ingenious conception, the formation of antitoxins is hence absolutely independent of the action of the toxophore elements on the cellular elements, and it suffices that these possess receptors or side chains capable of uniting with the haptophore groups of the toxin. This explains

why it has been possible to produce antitoxins from toxins which have lost some of their toxic properties, but which have preserved their property of uniting with antitoxic substances. Ehrlich gives the name *toxoids* to those modified toxins that have lost their toxophore groups, while the haptophore group, the producer of the immunizing substance, is still preserved intact.

According to Metchnikoff's theory, which is very similar, it seems quite possible that the phagocytes, thanks to the facility with which they absorb poisons, occupy an important place as producers of antitoxins. It has not been possible so far to verify this theory in our at present imperfect knowledge regarding this subject. The domain of immunity has, however, made brilliant conquests during these last few years, so that we should not despair of arriving at a definite solution before long.

In the vaccinated animal the antitoxin is reproduced, and it is possible to obtain several times, from the vaccinated animals, successive portions of antitoxic serum.* The protective power of these antitoxins is absolutely marvelous. An animal accustomed gradually to the tetanic virus yields a serum containing an antitoxin a thousand times more active than the virus.

* Ch. Salmonsen et Th. Madsen: Réproduction de la substance antitoxique. *Ann. Inst. Pasteur*, xii, p. 762. Roux et Vaillard: *Ibid.*, 1893, p. 83.

According to Vaillard, a quintillionth of a cubic centimeter of this antitetanic serum suffices to preserve one gramme of living mouse from the effects of a dose of tetanic serum that would otherwise be surely fatal.

In the animal, the antitoxins are eliminated mostly by the fluids of the body, and particularly by the urine. Ehrlich has demonstrated that they also pass into the milk, and this fact is confirmed by a large number of observers. It explains the immunity acquired by nurslings, and which is transmitted by the milk.

Serotherapy.—The search for antitoxins and their rôle in the etiology of infectious diseases are fundamental points in actual therapy. It has been demonstrated that the serums of certain vaccinated animals enjoy very extended antitoxic therapeutic properties; for instance, the serum of vaccinated rabbits is an antivenom towards erysipelas; and the sterilized cultures of the pneumococcus or of the Bacillus pyocyaneus prevents infection of carbuncle (anthrax).

The antivenomous serum of the ass immunized by injections of increasing doses of the venom of the terrible naja is a perfect prophylactic and curative, not only as regards the venom of this serpent, but also against that of the crotalus, trigonocephalus, and viper.

We shall take up the study of serotherapeutics in another volume of this collection.

PART II.

THE TOXINS PROPER.

CHAPTER III.

I. VEGETABLE AND ANIMAL TOXINS.

The vegetable toxins possess the characteristic property of being innocuous, and of being almost completely devoid of poisonousness, when they are absorbed by the intestines; we can see, from this, how greatly they differ from the poisons proper.*

The vegetable toxins known are quite numerous; nevertheless our knowledge regarding them is very incomplete. Our review of them will be chiefly descriptive.

Many of the leguminous plants are poisonous, either because of emanations exhaled by them, or by reason of their alkaloids, or because of some toxins contained in them. We shall commence with these.

Abrin.—This toxin, which was studied in par-

* It is understood that the active principles of mushrooms are not comprised under this definition, but they will be studied under the next heading.

ticular by Warden and Waddell,* then by Kobert † and de Hellin,‡ is found in the fruit of the Leguminosæ, Abrus precatorius (wild licorice, or jequirity). Its name was given it by Warden and Waddell, who discovered both its toxic nature and the vegetable toxin; the toxin is found only in the seeds. To extract it, the seeds are macerated in water, and the solution filtered and precipitated with alcohol; the precipitate which forms is collected and dissolved in distilled water, from which it is again precipitated by adding powdered ammonium sulphate. The precipitate is then collected and submitted to dialysis in order to eliminate the ammonium sulphate. The abrin so obtained forms an albuminoid substance § stable at 100° C., and possessing rotatory power; it liquefies starch paste, and is extremely toxic. One milligramme suffices to kill a rabbit within several hours. It must be observed, however, that, as is the case with all the toxins, abrin acts or kills only after a period of incubation which generally exceeds twenty-four hours.

It is possible to vaccinate an organism so as to withstand a lethal dose of abrin, but it requires quite a long time; it is effected by injecting into

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* Warden and Waddell: *Non-bacillar Nature of Abrus Poison.* Calcutta, 1884.

† Kobert: *Arbeit. aus dem Pharmak. Institut.* Dorpat, 1893.

‡ Hellin: *Inaug. Dissert.* Dorpat, 1891.

§ Ehrlich: Experiment. Untersuchungen über Immunität. *Deutsch. Med. Woch.*, 1891.

a suitable animal very small doses of the substance, and increasing the quantity gradually. Rabbits which have been rendered highly immune towards venoms are capable of resisting without inconvenience doses of abrin which are ordinarily fatal; and the blood serum afforded by them contains a specific antibody for the substance.

Ricin.—This vegetable toxalbumin has been studied particularly by Stillmark,* by Dixon,† and Thuson.‡ It is found in the seeds of the castor plant; three or four of the seeds suffice to cause a gastroenteritis accompanied by serious symptoms and even by death.

It was first isolated by P. Ehrlich, by treating the seeds with lukewarm water, and precipitating the aqueous solution with alcohol. The toxalbumin is soluble in water, but on boiling the solution, the substance loses in great measure its activity.

Ricin possesses considerable activity. 0.00003 Gm. suffice to kill a rabbit when injected hypodermically; 0.2 Gm. are fatal to man. The action is not immediate, but follows a period of incubation. Ehrlich has shown that, exercising precaution, it is possible to create, as with abrin, a condition of tolerance or habituation, and in consequence to cause the formation of a specific antibody.

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* STILLMARK: *Arbeit. aus dem pharmacol. Inst. Dorpat*, 1889.
† DIXON: *Austr. Med. Gazette*, 1887.
‡ THUSON: *Journ. f. prakt. Chem.*, XCIV, p. 444.

Robin.—This toxic albuminoid was obtained from the bark of an Acacia (Robinia Pseudacacia) by Power and Cambier,* by exhausting with water at a temperature of about 30° C., and precipitating the infusion with alcohol. The substance is analogous to ricin, and like this, possesses powerful toxic properties.

Toxicity of the Vegetable Diastases.—The diastases, which have been treated of in a volume of the Encyclopédie Léauté,† and to which we would refer the reader who is desirous of more complete details, develop powerfully energetic toxic properties when injected into the organism. Thus *amylase* causes, when injected subcutaneously, a considerable rise of temperature, but without any other toxic symptoms. *Invertin* or *sucrase* was studied by Roussy under the name *pyretogenin*, but it appears probable that this diastase was not the only substance present in the product, but that there were present reducing diastases, as we have already shown in the first volmue of this collection, devoted to the phenomena of reduction within the living organism.

The pyretogenin of Roussy gives rise to an attack of violent fever, but it loses all activity when heated to 80–100° C.

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* Power and Cambier: *Pharm. Journ. and Transact.*, 1890.

† Pozzi-Escot: *Les Diastases et leurs Applications.* Masson, 1900.

Through his researches, Roussy clearly demonstrated,* for the first time, that the fever may cause the formation within the blood of a substance clearly belonging to the class of soluble ferments or zymases. Now, it is well known that within the animal economy there exist many ferments of this character; and experiment has shown that they can, at a given period and under various influences, leave the cells in which they are normally localized, pass into the blood plasma, and reach the nervous centers, where they cause serious effects. We have already dwelt upon the mechanism of autointoxication of the organism. The toxic action of certain digestive diastases has been shown by Hildebrandt, who has demonstrated that 0.1 Gm. of pepsin is capable of killing a rabbit in two or three days.

II. TOXINS FROM MUSHROOMS.

Mushrooms are alimentary substances of the highest order, causing a general stimulation of the entire organism. The substances met with belong, according to their composition, to different classes—celluloses, sugars, and amylaceous substances, alcohols, acids, fats, astringents, essential oils, resins,

* Roussy: *Aperçu historique sur les ferments et fermentations.* Paris, 1901. J. Rousset, publ.

alkaloids, and albuminoids. The study of the last only, the albuminoids and diastases, interests us here. The most important of these albuminoid substances, *phallin*, was discovered in 1890 by Kobert. Pouchet also has isolated a whole series of other toxic albuminoids, particularly from Amanita muscaria (Fly Agaric).

There are alimentary as well as toxic species in every possible variety among mushrooms, some species consisting chiefly of the edible kind, others consisting of the poisonous variety.

In consequence of the toxicity of mushrooms, great attention must be given to the treatment to which they are subjected when it is desired to utilize them for alimentary purposes. Thus the toxic principles of several varieties can be removed, and the mushrooms rendered edible by very simple means.

Pouchet has made a very ingenious comparison between the ethereal, alcoholic, saline, and aqueous extracts of mushrooms, and bacterial cultures. The analogy is striking as to the presence of toxin, toxalbumose, and albumoses more or less toxic; it is moreover not exaggerated, since, according to the classification generally admitted, mushrooms are nothing more than the very advanced representatives of a group the more simple members of which constitute the bacteria.

The same author has shown that phallin obtained

from the juice of the Fly Agaric will kill a guinea-pig weighing 600 grammes in one hour.

As we have already stated, it is the phalline to which the ordinary disorders which mushrooms cause are due. According to Kobert, a 1 : 250 000 solution of this substance causes an intense hemolysis, with all its disastrous consequences.

According to Pouchet, the flesh of mushrooms must be compared with meat that has been kept for some time to become tender, and it is well known that though this "tendering" process renders the meat more digestible, it may also allow the meat to acquire noxious properties, due to the presence of toxins.

Phallin is the type of those toxic albuminoids of unknown composition which exist in mushrooms, and which are comprised under the name *sapotoxins*. The intravenous injection of phallin into an animal, in the proportion of 1 part to 1 000 000 parts of body weight, causes sudden death within one minute; in the proportion of 1 : 5 000 000, death occurs in about three minutes; in the proportion of 1 : 50 000 000, death also occurs, but is greatly retarded. An injection of 0.0005 Gm. per kilo of body weight of animal causes solution of the blood corpuscles to such an extent that thirty minutes later the blood serum is strongly colored red, as well as the veins.

Instead of being easily altered under the influ-

ence of an elevated temperature, as are many of the albuminoid substances, whereby their toxic power is lost, phallin may be boiled for half an hour with water without undergoing any noticeable alteration. Pellegrini has observed that the dried juice of Amanita Phalloides (Death-cup) preserves its properties for more than a year.

According to a recent paper by Gillot, the symptoms of poisoning by mushrooms must be ascribed to albuminoids (phallin and albumose), alkaloids (muscarine, choline, or betaine), or to resinoids (cambogic and agaricic acids).

The *alkaloids* found in mushrooms are: *Muscaridine* (an oxyneurine), which possesses considerable toxicity, and of which 0.00005 Gm. suffices to kill a frog; *neurine* (trimethylethylammonium hydroxide); *choline* (trimethyloxyethylammonium hydroxide); *mycetomuscarine; anhydromuscarine* (an oxyneurine); and a whole series of various betaines.

Symptomology.—It is quite natural to divide this symptomology into three different periods; that of incubation, that of manifestation of symptoms, and that of termination.

The duration of the first period, that of incubation, is exceedingly variable; it very rarely lasts more than forty-eight hours, and becomes general only a few hours after absorption. Certain conditions influence the duration; firstly the quantity of mushrooms ingested, then the manner in

which they were prepared; and, to some extent, the nature of the organism, whether child or adult, healthy or in poor health.

When it is a question of the more particularly alkaloid-containing mushrooms, especially when the poisoning is due to muscarine, the toxic symptoms generally develop rapidly, the first symptoms appearing about one hour after the ingestion of the mushrooms. On the other hand, if the poisoning is due to one of the albuminoid group, and particularly in the case of phallin, the period of incubation is longer, and may last ten, twenty, thirty, or even forty-eight hours and more.

The symptoms begin with dizziness and an indefinable sensation of being ill.

The second period is characterized chiefly by digestive and by nervous derangements. The digestive derangements are evidenced by very violent and painful vomiting, and diarrheas of choleraic or dysenteric character. The nervous derangements vary according to whether they are developed by an alkaloid, which causes delirium with hallucination, or by albuminoids, which cause depression, ataxo-adynamia, and stupor, these being particularly characteristic of the action of the toxic albuminoids.

As for the period of termination, it results either in death or a cure. If the poisoning is due to phallin, death appears to be an almost inevitable con-

sequence, as it occurs in 80 per cent. or more of the cases. The poisoning by the alkaloids is less dangerous, and the cure, when it does occur, is very rapid, almost immediate, in fact, while in the case of the toxic albuminoids the cure is very slow, and attended by relapses.

One characteristic of these toxalbumins is that they are apt to develop specific antitoxalbumins. This fact has been verified not only in the case of abrin, ricin, robin, and their analogues, but also in that of the vegetable and animal diastases possessing toxic properties even in the slightest degree only. These antibodies generally exhibit their action *in vitro*. Thus antiricin exerts its antiagglutinative action on the erythrocytes *in vitro* in a saline medium in which the erythrocytes cannot live.

Here, again, as in the case of the antitoxins, it must be admitted that the antitoxalbumin possesses a specific affinity by virtue of which it unites chemically with the toxalbumin to give rise to a new substance which is devoid of toxicity.

The first antidiastase obtained by immunization methods, and according to the mechanism we have already seen, was *antiemulsin*, obtained by Hildebrandt.* This antiemulsin counteracts, both *in*

* Hildebrandt: Weiteres über hydrolyt. Fermente, etc. *Virch. Arch.*, cxxxi, 1895, p. 5.

vivo and *in vitro*, the specific action of emulsin. These studies have been followed by a large number of scientists, particularly by Camus and Gley,* Carnot, Mesnil,† and Charron and Levaditi,‡ in the case of trypsin; and Sachs § in the case of animal pepsin. Gessard ‖ obtained a very active *anti-tyrosinase*, and Mohl an *antiurease*.

The most important researches regarding this subject have been published by Morgenroth, Briot,¶ and Korschum** on *antilab* (or *antirennet*). The researches of these authors have fully demonstrated that there is considerable difference between the various rennets, which had heretofore been confounded under one head; thus there is no difference whatever between animal rennet and the rennet extracted by Rosetti †† from Cynara cardunculus (cardoon) so far as their coagulant action on milk is concerned, yet each yields an antibody which is strictly specific to itself. From a scientific point

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* Camus and Gley: *Compt. rend. de la Soc. de Biolog.*, 1897.

† Mesnil: Sur la digestion des actinies. *Annales de l'Institut Pasteur*, 1901.

‡ Charrin and Levaditi: *Compt. rend. de l'Académie dest Sciences*, 1900.

§ Sachs: Ueber Antiseptika. *Zeitschr. f. Biolog.*, 1901, xxvi.

‖ Gessard: *Annales de l'Institut Pasteur*, 1901, p. 609; *Comp. rend. de la Société de Biologie*, May, 1902.

¶ Briot: Thèse de Doctorat ès-Sciences, Paris, 1900.

** Korschum: *Zeitschr. f. physiolog. Chemie*, 1902, xxxi.

†† Rosetti: *L'Orosi, giorn. di chemica, farmacia et scienza affini*, 1898.

of view we see, therefore, that the preparation of antidiastases permits us to differentiate certain diastases that could otherwise not be differentiated.

III. ANIMAL TOXINS.

As we have shown at the beginning of this chapter, certain diastases, and particularly those that are concerned with the digestive processes, pepsin, trypsin, etc., and which are produced in abundance by the entire living organism, possess quite clearly defined toxic properties, and sometimes to even a considerable extent.*

Hemialbumose, from which peptones are formed, is itself a dangerous toxin. It is generally believed that the toxic action of the peptones and of the products of digestion of the albuminoids is due not to the peptone itself, but to the more advanced products of digestion, alkaloidal products unquestionably closely allied to the ptomaines.

Nevertheless, the true peptones behave just like true poisons, when they are introduced hypodermically into the blood.†

Brieger has made us acquainted with a non-proteid substance, under the name of "peptotoxin," which is met with at the beginning of the putre-

* Gustave Saux: De la toxicité des produits de la digestion peptique. *Thèse de doctorat*, Bordeaux, 1902.

† Schmidt: *Mühlheim, Arch. de physiol.*, 1880.

faction of albuminoids. This toxin, which is not a protein, is nothing else but a ptomaine. It is not altered by heat, and possesses a very high toxicity. Brieger claims that it is a hydroxylized derivative of an aromatic amide.*

Besides these facts, experiment has shown that the leucocytes, or white corpuscles, the defensive rôle of which we have noted in phagocytosis, owe their properties to the ferments which they secrete, and particularly to some of the digestive ferments. These white corpuscles are very rich in ferments of all kinds. Rossbach found in them amylase; Achalme found lipase, casease, and trypsin; and the study of immunity has brought to light a series of other ferments, the alexins or cytases (microcytase and macrocytase), which have an exceedingly important rôle to play.

It may easily be conceived that under certain circumstances a part or the whole of these ferments can pass into the blood of the fluids of the body, when they give rise to serious disturbances in certain cases, or confer immunity in others.

It is thus that, according to Gautier, the rise of temperature which characterizes fever is a consequence of the abnormal transudation of these normal ferments into the blood, and their trans-

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* BRIEGER: *Berichte d. D. chem. Gesellsch.*, XIX, p. 3120; and *Verhandl. d. Congress f. innere Med.*, II, p. 277.

mission by the general circulation to the nervous centers.

However, it is not only in the leucocytes that we meet with these toxic digestive ferments; it appears quite probable, and has even been partially demonstrated, that they occur in a large number of other cellular elements.

It is not necessary here to dwell upon the formation of the antibodies of this group of active substances. The animal toxins are animal diastases, and we have seen in the preceding paragraph that these substances yield specific antibodies with great facility. For the rest, we will dwell more fully on these antibodies of the animal toxins in another volume of this collection, specially devoted to the study of these substances, and entitled "*Les Serums Immunisants*," to which we refer the reader who is desirous of obtaining more complete details than he can obtain in the present volume.

Alimentary Intoxications. — What we have already stated permits us to understand the phenomena of indigestion and botulism. The toxic substances form within the digestive tract when the nervous conditions modify the composition of the gastric juice, and arrest the flow of hydrochloric acid, the presence of which normally checks the development of the microbial flora, so rich within the stomach. The result is the production,

within the organism, of all kinds of dangerous toxins. The same thing happens when the liver does not functionate normally, and this affords us a knowledge of the mechanism by which foods that are most wholesome may become toxic by reason of poor digestion or poor assimilation.

The absorption of spoiled viands may, *a fortiori*, produce serious results. The alteration may be due not only to a bacterial infection, as in tainted meat, but it has also been proved that the flesh of an animal that has died of terror or madness may be very dangerous as a food, even after cooking, because, although there are toxins which are destroyed by a sufficient heat, there are ptomaines and certain toxins that resist destruction under these conditions.*

The use of preserved but spoiled beef, preserved ham or birds, sausages frequently, and pieces of pork tainted by sausage poison, gives rise to a succession of toxic symptoms the principal ones of which are dryness, constriction of the pharynx, bilious vomiting, diarrhea, dyspnea with pulmonary edema, etc. Fish and eggs are foods quite frequently capable of developing serious results; the same is the case with molluscs, mussels, oysters, lobsters, and snails. Lastly, moldy bread, spoiled cheese, putrid water, and spoiled vegetables them-

* POLLIN and LABIT: *Examens des aliments suspects*, Masson, publisher.

selves, are proper agents for determining attacks of botulic poisoning.

We have seen, at the beginning of this volume, that putrid meats contain ptomaines, which are among the most toxic alkaloidal bases. We have shown that Brieger has isolated from them neuridine, putrescine, muscarine, and guanidine; that Nencki has isolated hydrocollidine; and that Gautier and Etard have obtained from them parvoline—only to mention a few of them.

Lastly, there may develop within the gastro-intestinal tract dangerous putrefactions, the products of which may enter the veins and arteries from the ileum (a portion of the small intestine) and be distributed throughout the organism. Although such poisonings occur, they do not immediately follow the ingestion of the spoiled or toxic foods, but they are always preceded by a period of incubation varying from several hours to several days.

These alimentary poisonings are recognized by a great physical depression, accompanied by vomiting and paralysis of the lower extremities, sweats, and diarrheas. In some cases there occur cutaneous eruptions; and when death happens, this occurs only several days later, and generally without being preceded by any great pain.

Urinary Toxins.—As we have already remarked several times, it is by the renal way that the organism voids its principal waste products.

We have seen also that it is by the kidneys that the toxins are eliminated in all pathological conditions. As a general rule, the urines are always more or less toxic. This toxicity of the urines must be attributed in the first place to the crystallizable organic principles (ptomaines and leucomaines*) which they contain; secondly, to the non-crystallizable † extractive matters not so well known; and lastly, to the saline substances, among which the potassium salts are the most active. We find these mineral salts particularly abundant under normal conditions in the urines of the herbivora. According to Bouchard, 0.18 Gm. of potassium chloride are sufficient to prove fatal to 1000 Gm. of living organism; a man excretes on the average 2.5 Gm. of this salt, and a rabbit excretes about double this quantity, weight for weight.

A very large number of hypotheses have been advanced regarding the toxicity of the urines. Wilson considers the urea as being responsible for it; Stadthagen‡ believes it to be due to the potassium salts, etc. Bouchard§ was the first to recognize that the toxicity of the urines is due to a number of causes. We will not dwell further on these active principles which, in the last analysis,

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* Adduco: *Arch. Ital. de biolog.*, 1891.
† Pouchet: *Thèse de Doctorat en Médecine*, Paris, 1878.
‡ Stadthagen: *Zeitschr. f. Klin. Med.*, xv.
§ Bouchard: *Leçons sur les Autointoxications.*

are no other than those that form in the various portions of the organism, and which are eliminated by the urine.

It is self-evident, and it has already been shown, that the toxicity of the urines varies greatly according to the malady, in consequence of the elimination of toxins by the urines. According to Bouchard, in infectious maladies the urines are twelve times more highly charged with toxins than is blood serum. Moreover, the toxicity of the urines is considerably augmented the moment there is the least febrile condition, no matter what the cause is.*

Even in the normal condition, the urinary toxicity varies greatly; and this is easily conceived since the physiological phenomena that control this secretion undergo incessant rise and fall. Thus, for example, the urines eliminated during sleep are less active than those produced during waking, because during sleep the elimination of cellular poisons is at a minimum. Exercise, walking, physical and intellectual labor, exert their portion of influence on these oscillations of toxicity; and this variation of toxicity is due not to any one variation in the mineral extractive matters, but rather more or less to the organic toxic products. We will not dwell further on this subject, but will

* Regarding this point see the excellent work by A. CHARRIN: *Poisons de l'Organism.* Masson, publ.

simply refer to the work by Charrin, already mentioned, for all supplementary details.

Autointoxications.*—The cells of the organism having, as a whole, a life very much like that of the microbes, it is quite natural that among the excreted products of the living tissues there should be found the same substances formed as a result of the anaerobic fermentation of albuminoids. Experiment has demonstrated that this is so, and Armand Gautier has irrefutably proven the existence of these principles.† Bouchard was the first to demonstrate the toxic nature of muscle extract,‡ and Roger § established the fact that the toxicity of this extract is due to ferment-toxins; it has since been recognized that after death these toxins accumulate in the muscles.

The extract of kidney made rapidly by cold process by triturating the washed kidney with glycerin, and precipitating the glycerinic solution with alcohol, contains toxic ferments to which the name "*hystozymes*" has been given.‖ These ferments split up hippuric acid into benzoic acid and glycocoll. Lépine has likewise discovered in the

* Ch. Bouchard: *Des Autointoxications.* Paris, 1887.

† *Bull. Acad. de Médecine* (2), x, p. 947, and xx, p. 115.

‡ Bouchard: *Leçons sur les Autointoxications*, Paris, 1887.

§ Roger: Toxicité des Extraits des Tissus Normaux. *Soc. de Biolog.*, 1891, p. 728.

‖ It is well to recall here that the kidneys contain both reducing and oxidizing ferments, as has been demonstrated by de Rey-Pailhade, and later by Abelous and Gérard.

kidney a very toxic pyrogenic substance.* Roger has given us evidence of the toxic properties of the liver, washed and pulped, and then sterilized by filtration through a porous diaphragm. This scientist has shown that the toxic properties are due to albuminoids, which lose their activity when heated to 100° C.†

It must be remarked that the organs we have studied are essentially reducers, and that the more powerful reducers yield the most toxic extracts. We find here a confirmation of Armand Gautier's views regarding the anaerobic origin of the toxic substances formed within the organism.‡

Blood serum precipitated by alcohol affords products which possess very marked toxic power. It would appear that the toxic products we speak of here are thermogenic diastatic substances derived from the white blood corpuscles. In certain diseases the blood serum may acquire a high degree of toxicity. We will recur again presently to this property as a normal characteristic of the blood of various animal species, and will study it in greater

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* Lépine: *Compt. rend. de l'Acad. des Sciences*, May 13, 1889; *Soc. de Biol.*, 1891, p. 724.

† Roger: *Compt. rend. Soc. Biol.*, 1891, p. 727.

‡ Pozzi-Escot: *Compt. rend. de l'Acad. de Médecine* (3), xlvii, p. 400. See also Pozzi-Escot: *État actuel de nos Connaissances sur les Oxydases et les Réductases*. Dunod, publ., Paris, 1902.

detail in a future volume of this collection, devoted to the immunizing active principles.

Glandular Secretions.—On studying the venoms we will see that a certain number of these products are the result of glandular secretion. This is a general property of the glands; and it was Brown-Sequard who first drew attention to the rôle played by these glands, and to the importance of the products that they throw into the blood.*

P. Noel showed later that the testicular juice possesses a high degree of activity, which he attributed to an oxidizing ferment, and which we have already mentioned, *spermine*.

The greater number of the other glands contain proteid matters and various peptones, more or less toxic, with amides and alkaloids.

Particular mention must be made of the thyroid gland, the secretions of which exercise a powerful action on the nervous centers and on nutrition.† It appears reasonable to attribute to the secretions of this gland a very powerful antitoxic action, and the first proof of this fact is that the organisms deprived of this gland become the seat of serious derangements; the urines of such organisms become particularly toxic, while, on the other hand, the hypodermic injections of the aqueous extract of

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* *Compt. rend. de l'Acad. des Sciences*, CXIV, pp. 1237, 1318, 1399, and 1534; CXV, p. 375; and CXVI, p. 856.

† LAULANIÉ: *Compt. rend. Soc. de Biol.*, 1894, p. 187.

the gland, when the derangements spoken of exist, cause the immediate disappearance of the derangements caused by the excision of the gland.*

Attempts have been made to isolate the active principle of the glands. Notkine isolated a *tyroprotcid*,† which is not sensibly toxic to animals who still retain the gland, but which becomes toxic when the gland is excised. It seems probable, however, that this product is not the principal agent of the thyroid gland.

From the researches of Schaeffer, Roos, and Sigmund Fraenkel ‡ it results that the active principle of the gland is not a toxin, but a purely chemical substance, a true leucomaine, which has received the name *thyroantitoxin.*

On the other hand, Baumann quite recently extracted from the thyroid gland an iodized substance, which he named *thyroiodine.*§

The suprarenal capsules also possess properties that have often attracted the attention of physiologists during the last few years. They are considered as being, just like the thyroid gland, producers of antotoxins; they destroy, or seem to

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* Gley: *Compt. rend. Soc. de Biol.*, 1891, p. 250.

† *Semaine Médicale*, Apr. 3, 1895, p. 138.

‡ *Wiener Med. Blätter*, No. 48; and *Gesellsch. d. Aerzte in Wien*, Nov. 22, 1895.

§ *Zeitschr. f. Physiol. Chem.*, XXI. pp. 319 and 481; and XXII, p. 1. Armand Gautier: Chimie Biologique, 2d edit., pp. 330–332. Masson, publ.

destroy, toxins that are artificially introduced into the circulation.

Albanêse * maintains that the function of the suprarenal capsules is to neutralize neurine, the toxic product of the disassimilation of the nervous system; this view, however, is opposed by Boinet† and Langlois.‡ On the contrary, it has been definitely proven that the suprarenal glands exert a specific action on the poisons of muscular origin. Abelous and Langlois § have in fact demonstrated that the alcoholic extract of the muscle of a decapsulated animal has the same properties as the extract of tetanized muscle; the decapsulated animal gives ergographic tracings analogous to those afforded by tetanized animals. The removal of the suprarenal capsule from an animal brings results, hence, analogous to those of fatigue—that is to say, that the toxic substances which accumulate as a result of the decapsulation resemble those that result from muscular exertion. The suprarenal capsules exert their action furthermore on other toxic products as well, as Guieysse‖ has shown, and particularly on the exogenous poisons. In

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* Albanèse: Recherches sur les fonctions des capsules surrénales. *Arch. Italiennes Biol.*, 1892.

† Boinet: *Compt. rend. Soc. de Biol.*, Mch. 1896.

‡ See *Compt. rend. de Biol. et Arch. Physiologie*, 1891–1897.

§ Langlois: Thèse de doctorat en Méd., Paris, 1897.

‖ Guieysse: *Les capsules surrénales du cobaye*, Thèse, Paris, 1901.

conclusion, it may be said that the matter concerns a most important rôle, and we cannot do better in this respect than to refer the reader to the memoir presented by Sergent and Bernard to the Académie de Médecine in 1902 and entitled *l'Insuffisance Surrénale.**

* Encyclopédie Léauté, cccxiv, Masson, publ., Paris, 1904.

CHAPTER IV.

THE MICROBIAL TOXINS.

THERE is but one way of characterizing the toxic poisons secreted by microbes, and that is to apply to them the name of the microbes generating them; thus the soluble and toxic poison of the tetanus bacilli has received the name *tetanus toxin*.

In toxic microbial cultures it is necessary to distinguish the toxins proper from the toxic alkaloids (ptomaines) which generally accompany them; this is easily accomplished by evaporating the solution in a vacuum at about 30° C., and then treating with alcohol and ether, in which the alkaloids are soluble, while the true toxins are insoluble. By fractional precipitation with alcohol it is easy to isolate the peptones and true toxins.

The microbial toxins possess two essential properties; one the pyogenic property, thanks to which the toxins first attract, then destroy the white blood corpuscles or leucocytes, and transform them into pus, and the other the pyretogenic property, which appears to belong only quite

indirectly to the pyogenic substance. The toxins in general retard the heart action.

We will not speak of the distinctions it has been sought to establish between the substances which possess these different properties, but will at once take up the discussion of several of the microbial toxins.

Anthrax Toxin * (from Bacillus Anthracis).—We will describe the preparation of this toxin as a type.

The cultures of the bacillus are made in Liebig's bouillon, to which has been added 0.1% of fibrin, the whole being carefully sterilized for a long time at 110° C. The cultures medium is inoculated with a drop of blood taken from the heart or spleen of an animal that has died of anthrax. At the end of a week, the culture is filtered, and the filtrate acidulated with a little acetic acid and precipitated by adding powdered ammonium sulphate. The flocculent precipitate is collected, washed, dissolved in distilled water, and dialyzed. The dialyzed solution is concentrated in vacuo at 40–45° C., and precipitated by adding to it alcohol. The precipitate formed is then collected and dried.†

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* Arloing, Cornevin, Thomas: *Le Charbon Symptomatique*, 1st edit., Paris; and Le Dantec: *La Bactéridie du Charbon*, Masson, publ.; Straus: *Le Charbon des Animaux et de l'Homme* Paris, 1887.

† Hankin: *British Medical Journal*, Oct. 12, 1889, and July 12, 1890.

In this manner there is obtained a grayish-white substance which is soluble in water, and which is fatal in large doses, but which, given in repeated small doses, confers immunity against anthrax.

According to Hankin, it seems that the toxic property of this toxin is due to an albumose.

Marchoux * has been able to confer immunity upon sheep by injecting first small quantities of the filtered culture of the anthrax bacilli, and then the virulent anthrax itself.

The animals thus rendered immune yield a serum which may be used as a vaccin against anthrax, and which even possesses curative properties under certain conditions.

In every case the acquired immunity is only temporary. We will recall to recollection the method employed by Pasteur for vaccinating against anthrax, using attenuated cultures, a method which is practiced daily at the present time.†

From the cultures of symptomatic anthrax (Bacillus Chauvæ) Chauvée extracted a very active toxin which can withstand without impairment a temperature of 110° C.‡ Roux § has shown that

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* *Annal. Instit. Pasteur*, IX, p. 785.

† CHAMBERLAND: *Le Charbon et la Vaccination Charbonneuse*, Paris, 1887. PETERMANN: *Annal. Instit. Pasteur*, VI, p. 32.

‡ DEUTSCHMANN: *Annal. Instit. Pasteur.*, VIII, p. 403.

§ *Annal. Inst. Pasteur*, Feb. 1888.

the serum of animals that have succumbed to the symptomatic anthrax is capable of vaccinating against this disease; we have here a new proof that the antitoxin is in fact a product of the defense of the cells of the organism, and the author mentioned has been able to vaccinate guinea-pigs by injecting into the peritoneum culture bouillon sterilized by heating to 115° C. or by filtering through porcelain.

Tubercular Toxin. — The culture bouillons of Koch's bacillus contain one or more active substances which constitute, and which is at the present designated as, tuberculin.* Koch's therapeutic tuberculin is obtained by evaporating to one-tenth its volume a culture bouillon of Koch's tubercle bacilli prepared from a 4-per cent. glycerinic mutton bouillon, and filtering through porcelain. By fractional precipitation it is possible to obtain from the crude tuberculin so prepared a product which is considered as pure tuberculin, and which possesses considerable activity.

Prolonged boiling on the water-bath completely destroys the activity of this tuberculin, which moreover hardly ever keeps longer than three weeks. It has been found possible to preserve it for an indefinite period, however, by adding to

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* Auclair: *Thèse de doctorat*, Paris, 1897; and *Arch. de Médecine*, exp. 1898.

it 30 to 40 per cent. of glycerin. It possesses all the general reactions of albuminoids.

Tuberculin is not toxic in the proper sense of the word. Injected in small quantities into the healthy human being * and into healthy animals, it exerts no effect; on the other hand, however, in tubercular organisms, even in incipient stages of the disease, even where it is almost impossible to make a clinical diagnosis, the injection of very small quantities develops a lively and characteristic reaction.†

Grasset and Vedel consider the tuberculin as an excellent means of diagnosing tuberculosis in man, but in such a case it is necessary to operate with the greatest caution, with very small quantities of the tuberculin, and to feel, in some sort, the sensitiveness of the patient, particularly in the case of children.

It is chiefly for the diagnosis of tuberculosis in cattle, however, that tuberculin is valuable. Thanks to Nocard, the procedure has to-day become a common practice. The injection of a fairly large dose, 0.3 to 0.4 Gm., according to the size of the animal, causes, in about ten hours or so, if the animal is tuberculous, a strong febrile reac-

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* Koch: *Deutsch. Med. Woch.*, Nov. 13, 1890–1897, No. 14, p. 209.

† *Annal. de l'Instit. Pasteur*, v, p. 191; *Arch. de la Soc. Biol. de Saint-Pétersbourg*, I, p. 213.

tion with an elevation of temperature of 1.5 to 3° C., whereas if the animal is not tuberculous no such reaction takes place.

Cases in which tuberculosis is far advanced, and in which the organism is impregnated with tuberculin, do not react after the injection of tuberculin.*

Tuberculin does not confer immunity, and the bacillus retains all its virulence, even in injected tissues; nevertheless, the return to health of animals in which injections have been recently made may be due to the action of large doses of the serum; and on the other hand the tuberculin, in large quantities, may render the location unsuitable for the development of the tubercle bacilli.

Diphtheria Toxin.—The most characteristic property of the diphtheria bacillus is the production, in culture media, of a special toxic substance which has been named *diphtheritic toxin*; this name, however, has come to be also extended to a liquid in which the bacilli have lived, and which has been sterilized by filtration or by any other suitable process.

Roux and Yersin † were the first to affirm that diphtheria is an autointoxication caused by a very active poison formed by the microbe in the restricted locality where it develops. In order to obtain this

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* Nocard and Leclainche: *Les Maladies Microbiennes des Animaux.*

† *Annal. de l'Instit. Pasteur*, II, p. 632, and VIII, p. 611.

toxin * a culture of the bacillus is first made in a mutton bouillon made strongly alkaline with sodium carbonate (10 grams per liter), and with the addition of 2 per cent. of peptone. At the end of about one month, the culture being kept at about 37° C., the liquid is filtered through porcelain. It is indispensable to employ a very virulent bacillus; it is hence frequently advantageous to increase the virulence and toxigenic power of the bacilli it is desired to use.

The toxic liquid obtained is exceedingly powerful: 0.1 Cc. kills a rabbit in forty-eight hours. This toxin is very sensitive to the effects of heat. When heated to 65° C. it loses almost all its toxicity; at 70° C. it becomes innocuous; and it only requires to be heated to 100° C. for fifteen minutes in order to lose all immediate activity even in large doses. Nevertheless toxins thus weakened are capable of proving fatal to an animal even after five or six months.

Light, oxygen, ozone and all oxidizers destroy the active principle of the diphtheria toxin, which is, moreover, rendered almost inactive by organic acids.

This toxin is capable of diffusing through animal membranes, a fact that is in agreement with the toxic effect seen in a subject attacked with diph-

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* See SPRONK: *Annal. de l'Instit. Pasteur*, IX, p. 785; *Ibid.*, X, p. 333; MARTIN, *Ibid.*, XII, p. 26; SPRONK, *Ibid.*, XII, p. 711.

theria, and due to the toxin passing through the mucosa. In spite of this property, however, the diphtheritic poison may be taken into the stomach without any pernicious results.

Roux and Yersin have shown that, like all the diastases, it may be precipitated from its solutions by the development, within these, of certain precipitates, particularly calcium phosphate. It is precipitated from its solutions by alcohol, as has been observed also in the case of diastatic solutions. All the toxic substance is contained in the albuminous precipitate thus obtained; but the prolonged action of alcohol, or repeated successive precipitations, alter it finally. Diphtheria toxin is likewise precipitated by the reagents for albumoses, particularly sodium sulphate in saturated solution. This procedure has been utilized by Brieger and Fraenkel for preparing the pure toxin, which they obtained in the form of very light, brilliant white, amorphous flocks, affording all the principal reactions of the soluble albumoses (biuret, xanthoproteic, Millon's), and which they characterized as a toxalbumin.

On injecting into healthy animals this diphtheria toxin attenuated by sufficiently heating at 70° C., employing at first small doses, and gradually increasing, it is possible to immunize them against diphtheria, as was first demonstrated by Carl Fraenkel.

Roux and Martin, who have specially studied this procedure,* have shown that a horse may be easily immunized by injecting into the animal the toxin diluted with a third of its volume of Gram's iodine solution, and in successively increasing doses. The initial dose is 0.25 Cc.; then, after two days, 0.5 Cc. of the same toxin is injected, and in like manner the dose is increased up to the eighteenth day, when the pure toxin is injected, at first in small doses, which are gradually increased so that at the end of two or three months injections of 80 Cc. of the pure toxin may be given without danger; the animal is then completely immunized.

The serum of an animal rendered immune in this manner contains a diphtheria antitoxin which possesses high power. A guinea-pig which has received an injection of 0.01 Cc. of the antitoxin is perfectly capable of withstanding a lethal dose of 0.5 Cc. of the toxin. The antidiphtheria serum thus obtained, and in almost limitless quantities, from an immunized animal, is capable of saturating the therapeutic diphtheritic toxin, and has to-day taken rank in therapeutics as the most efficacious remedy in diphtheria. Injected in varying doses, it confers a temporary but immediate immunity.

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* Contribution à l'Étude de la Diphtérie. *Annal. de l'Instit. Pasteur*, VIII, p. 609; *Ibid.*, p. 640.

Nevertheless antidiphtheria serum must not be considered as an antidote; and in pathological diphtheria, the more serum is required the later it is used.* In certain cases, if employed too late, it may prove ineffective.

The preventive action of the serum is remarkable. In 10 000 inoculated cases Behring and Ehrlich have had but 10 cases of diphtheria, and these were, moreover, of a benign character. The duration of the immunizing action appears to be from three weeks to two months.

This diphtheria antitoxin was first prepared by Guérin and Macé † by adding to the antidiphtheria serum a large volume of alcohol, washing the precipitate, and drying it in a vacuum. It is soluble in water, and loses its activity when heated to 65° C. Wassermann ‡ has proposed to extract it from the milk of immunized animals, by first coagulating the milk by rennet in the presence of sodium chloride, filtering, and removing the fat from the clear liquid by means of chloroform. After decanting, the clear solution obtained is precipitated by adding to it 30 to 33 per cent. of ammonium sulphate. The precipitate is dried in a vacuum on a polished porcelain slab after having

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* Bayeux: *Thèse de Doctorat*, Paris, 1899.
† *Compt. rend. de l' Acad. des Sc.*, Apr. 5, 1895.
‡ *Zeitschr. für Hygiene*, XVIII, p. 235.

first been strongly expressed. It is then dissolved in water.*

Tetanus Toxin. — The fact that the tetanus bacillus never penetrates to the interior of the organism enabled us long ago to foretell that it secretes a very powerful toxin capable of dialyzing and diffusing through the economy. Kuno Faber was the first to fully recognize the fact that the culture bouillon of this bacillus, fully sterilized by filtration through porcelain, possesses an exceedingly high toxicity, and exerts a toxic effect on 50 000 000 times its own weight of living organism. Brieger had previously, however, extracted three ptomaines from the cultures of the bacillus — *tetanin*, *tetanotoxin*, and *spasmotoxin*.† In order to obtain a highly active liquid, the same culture medium is inoculated several times in succession, but filtering each time before the new inoculation; the microbes greatly increase in number after each fresh inoculation, and the toxic substance developed by them accumulates.‡

Experiment has shown that the culture bouillon thus obtained contains two kinds of toxic sub-

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* Roux and Martin: Contribution à l'Étude de la Diphtérie. *Annal. de l'Instit. Pasteur*, VIII, p. 512.

† Die Pathogenese des Tetanus. *Berlin. Klin. Wochenschr.* 1890, No. 31.

‡ Naillard: *Compt. rend. de l'Acad. des Sciences*, CXX, p. 1181.

stances *—highly toxic alkaloidal bases (ptomaines, tetanin, tetanotoxin, etc.), and a true toxin, possessing diastatic properties, and of almost incredible toxic power.

This toxin had already been isolated by Kitasato. It is a toxalbumin, and is very sensitive to the action of heat. A temperature of 65° C., maintained for 30 minutes, renders it quite inactive; and it becomes oxidized and is destroyed by the action of the air in the presence of light.

Brieger and Boer,† by precipitating with zinc chloride the filtered culture bouillon, obtained a pure, amorphous tetanus toxin, which they also considered as a toxalbumin, and which possesses exceedingly toxic properties.

If a precipitate be caused to form in these toxic solutions, as, for instance, a precipitate of calcium phosphate, this carries down with it all the toxin present in the liquid. 0.0005 Gm. of this precipitate is surely fatal to a guinea-pig.

Dozon and Cournemont have observed that even in doses of 300 to 400 Gm. of the filtered culture liquid, this toxin is not immediately toxic to a horse, but kills the animal only after a period of incubation of at least twenty-four hours. The blood of such an animal, however, is immediately

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* *Annal. Instit. Pasteur*, v, 15.

† *Deutsche Med. Wochenschr.*, No. 49, Dec. 3, 1896.

and directly fatal to animals into which it is injected.*

Experiment has shown that animals that have been cured of tetanus possess no immunity whatever against tetanus; nevertheless Behring and Kitasato † first, and Wassermann and Kitasato later on, succeeded in preparing a *tetanus antitoxin*. To obtain this, the immunization of the animal, horse or cow, is effected by injecting increasing quantities of the toxin, more or less attenuated by mixing it with Gramm's iodine solution; the immunization is easily and rapidly accomplished by the process devised by Roux and Vaillard.‡

The immunized animals yield a serum which, mixed with tetanus cultures, renders these innocuous, and which enjoys an antitoxic power that borders on the marvelous.§ A quintillionth of a cubic centimeter of the serum per gramme weight of a live mouse suffices to protect the animal from an otherwise fatal quantity of tetanus toxin.‖

This serum is nevertheless powerless to preserve man in cases of acute tetanus; it confers an immediate, but only transitory, immunity.

As to its mode of action, it appears to cause a permanent condition of excitation or of nutri-

* *Compt. rend. Soc. Biol.*, 1893, p. 294; *Ibid.*, 1894, p. 878.
† *Deutsch. Med. Wochenschr.*, 1890.
‡ *Annal. Instit. Pasteur*, VII, p. 64.
§ NOCARD: *Bull. de l'Acad. de Médecine*, Oct. 22, 1895.
‖ NAILLARD: *Compt. rend. de l'Acad. de Sciences*, CXX, p. 1181.

tive reaction of the cells, which makes these resistant to the poison. As in the case of the other toxins, the quantity of antitoxin necessary to protect an organism is so much greater the later the treatment is applied.

Mallein (Toxin of Glanders).—Among the soluble products secreted in the culture media by the glanders bacilli, there are found true toxins to which are ascribed certain symptoms of glanders infection. These toxins have been isolated and designated by the name *mallein*. First prepared by Helman and Kalmino, mallein was later on specially studied by Roux and Nocard, and, in consequence of the researches of the last-mentioned scientist, it has acquired great importance.* It is obtained by sterilizing at 110° C. cultures of the glanders bacillus made with mutton bouillon with the addition of salt, glycerin, and peptones. To isolate the toxin the culture bouillon is first sterilized by heating for half an hour in an autoclave at 100° C. It is then filtered, concentrated to one-tenth its volume on a water-bath, and filtered through a Chardin filter. The mallein is thus obtained in the form of a brown syrupy liquid containing half its weight of glycerin.

This solution keeps well when kept from air, light, and heat. In practice it is employed in 10-per

* NOCARD: *Les Maladies microbiennes des animaux*, Paris.

cent. solution in phenolated water (5:1000). The mallein may be precipitated from the crude solution by the addition of alcohol, as recommended by Foth. Foth's mallein occurs as a white, light powder, very easily soluble in water.

Mallein enjoys a very important rôle in veterinary therapeutics, a rôle analogous to that of tuberculin, permitting the diagnosis of incipient glanders.*

Experience has shown that in animals already attacked by glanders, even if ever so slightly, the thermic reaction never fails when 0.25 Cc. of the mallein solution is injected. In healthy animals, however, the injection of mallein, even in much larger quantities, causes no apparent effect. In animals attacked by glanders the reaction attains its maximum in twelve hours, and several days are required for the temperature to return to normal.†

According to Nocard, mallein possesses no immunizing properties whatever.‡

Typhoid Toxin.—This is obtained, like the other microbial toxins, from a culture, prepared with more or less difficulty, from Eberth's typhoid

* Strauss: *Arch. de Médic. expériment.*, 1886.

† Cadiot and Roger: *Compt. rend. Soc. Biol.*, 1895, p. 770; Wladimirow: *Arch. des Sciences Biol. de St.-Pétersbourg*, IV, p. 30; Bourges and Méry: *Soc. de Biol.*, Feb. 5, 1878.

‡ Galtier: *Compt. rend. de l'Acad. des Sciences*, XCII, p. 303; Strauss: *Arch. de Médic. expériment* I, p. 489.

bacillus. This toxin, injected into guinea-pigs, develops in them typhoid fever.

In the solution there occurs a ptomaine, which has been isolated by Brieger, and which gives rise to almost all the phenomena of typhoid fever; this ptomaine is called *typhotoxin*.*

The same author, in collaboration with Fraenkel,† later on isolated a toxalbumin from the culture bouillon of the typhoid bacillus. Sanarelli ‡ obtained an active toxin by macerating for several days at 60° C. a month-old culture of the typhoid bacillus made with a 2-per cent. glycerin-bouillon. Chantemesse has also published a process which yields a highly virulent toxin.§

Chantemesse and Widal ‖ have shown that on injecting into an organism increasing quantities of the sterilized cultures of Eberth's Bacillus, it is possible to fully immunize an animal against the bacillus itself, and even also against the Bacillus coli communis. The operation, however, is tedious and painful. The serum of immunized animals possesses preventive and curative properties respecting the effects of typhoid bacilli.

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* BRIEGER: *Microbes, Ptomaïnes et Maladies*, Doin, publ., Paris, 1887; LUFF: *Brit. Med. Journ.*, 1889.

† *Berlin. Klin. Wochenschr.*, 1890.

‡ *Annal. de l'Instit. Pasteur*, VIII, p. 103.

§ *Compt. rend. Soc. de Biol.*, p. 232, Jan. 30, 1897. *Congrès d'Hygiène de Madrid*, 1898.

‖ *Annal. Instit. Pasteur*, VI, p. 755; SANARELLI: *Ibid.*, p. 721.

A dose of the filtered culture, which is fatal to a guinea-pig, becomes innocuous when mixed with 0.5 Cc. of the serum of a vaccinated guinea-pig; 6 Cc. of the serum injected six hours after an injection of the virulent culture, hence when this is in full action, suffice to save the animal.* So far as the human being is concerned, the results obtained have not been sufficiently satisfactory.

The culture bouillon of the Bacillus coli communis, which is closely allied to Eberth's bacillus, also contains soluble toxic substances which have been named coli-bacillus toxin. This substance, which is produced only in small quantity by the microbe, is fatal only in very large doses.

Cholera Toxin.—Very little is known regarding the toxic products of the spirillium choleræ; nevertheless, the fact that typical cholera exhibits every symptom of the action of a toxic agent demonstrates quite clearly the elaboration of some toxic substance within the cultures of this microbe.

Villiers † found in it a liquid ptomaine; Klebs ‡ found another and crystallizable ptomaine; while Pitai discovered in it a toxin unalterable by heat, and which he considered as a toxopeptone. According to Gamaleia § there is present a true toxin,

* Funck: *La Sérothérapie de la Fièvre Typhoïde*, I, Brussels, 1896.

† *Compt. rend. de l'Acad. des Sciences*, Jan. 12, 1885.

‡ Klebs: *Allgem. Wien. Med. Zeit.*, 1887.

§ *Arch. de Méd. Expérim.*, IV, p. 173.

alterable by heat, and the reactions of which entitle it to be considered as a nucleo-albumin; he has also found in it a toxic nuclein.

These toxic substances are found, according to Gamaleia, Pfeiffer, and Sanarelli,* confined during the life of the microbe within its cellular envelope, and does not diffuse through this. Metchnikoff and Roux are of the contrary opinion,† however, and they have prepared a toxin almost insensitive to a temperature of 100° C., and precipitable from its solutions by ammonium sulphate or strong alcohol; the toxin is a toxalbumin. This toxin is quite toxic; one-third of a cubic centimeter suffices to kill 100 Gm. of guinea-pig in 18 hours; with larger doses, death is almost immediate.

By immunizing guinea-pigs, rabbits, and horses with this cholera toxin, Metchnikoff and Roux obtained a serum which is distinctly antitoxic for rabbits. Nothing absolutely certain has been found as to its action on man.‡

We will not dwell longer here on the toxins of microbial origin. It appears evident, however, from what has been stated above, that the great

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* *Annal. de l'Instit. Pasteur*, IX, p. 129.

† *Ibid.*, X, p. 257.

‡ HAFFKINE: *Compt. rend. de l'Acad. des Sciences*, 1892; METCHNIKOFF: *Annal. de l'Instit. Pasteur*, VII, p. 403; and ROUX: *Ibid.*, X, p. 253.

majority, if not all, of the virulent microbes manifest their virulence by means of toxic secretions. Almost every one of these toxins has been the subject of study. They would otherwise not have interested us here, where our main object was but to dwell upon the general properties.

CHAPTER V.

THE VENOMS.

General Nature of Venoms.—The venoms are more or less toxic products secreted by certain reptiles, batrachians, and fish; by a large number of invertebrates; by arachnids, apids, scorpionids, araneids, and a large number of other insects.

The venoms are toxic principles very closely allied to the microbial toxins; like the latter, they form two classes, the one alkaloidal, the other proteid, possessing a true diastatic character. They closely resemble the microbial toxins, moreover, by the fact that they are capable of being transformed into vaccins by attenuation of their virulence, by the action of heat or chemical reagents, and of leading to habituation of use and the conference of immunity.* Moreover, like the various viruses, the serum of immunized animals is antivenomous, so that if injected into the veins or beneath the skin of non-immunized animals, the

* *Annal. de l'Instit. Pasteur*, VIII, p. 281; *Journ. of Physiol.*, VIII, p. 203; and *Soc. de Biol.*, 1894, p. 111.

serum confers upon them an immunity against venom which lasts for some time.

These venoms, like the microbial toxins, possess but slight toxicity when absorbed via the stomach. Fraser, utilizing a method previously advocated, succeeded, by following this method, in vaccinating against serpent-venom by causing the absorption by animals of constantly increasing doses of venom.

It was thus possible to make the animals withstand doses a thousand times greater than the ordinary lethal dose; the blood and serums of these animals at this point possessed immunizing properties, and this property passed by heredity to the offspring, to which it is transmitted by the blood itself, and by the milk during feeding.

Along with these resemblances between the venoms and toxins, attention must be called to a very important difference. As we have already seen, the action of the toxins on the organism is always preceded by a certain period of incubation; the action of the venoms, on the contrary, is almost instantaneous, and in this respect they behave like chemical agents and alkaloidal toxins.

If the venoms are preserved in a moist condition, they change because they undergo putrefaction, which is generally the case with all diastatic substances, and particularly the toxins.

It is interesting to note that animals which have been bitten by a venomous serpent, but which,

for some reason or other, have not succumbed to the venom, never recover their former condition; if they were young, their functions cease to develop, and they droop; if they are adults, their general condition remains that of stupefaction.

Venomous Serpents.—Among the venomous serpents,* the most important as well as the most dangerous are the following: Cobra di capello (Naja tripudians, the hooded cobra) and its analogues, the black Naja, Naja hagé, etc.; the elops (coral serpent); the bungurus of Bengal and Burmah; the Platycercus proteroglyphia, which is found chiefly in the waters of the Indian Ocean; the crotalian solenoglyphs of the two Americas, and among which in particular are the rattlesnake, the fer-de-lance (the yellow viper) of Martinique; the surucucu of Guiana; and the moccasins and copperheads of Texas and Florida. Lastly, the entire group of viperian solenoglyphs, among which are the Echidnæ, the bite of some of which, for instance the daboia or echidna, is dreadful; the African vipers, among which may be mentioned the horned viper, the bite of which will kill a camel; the springing viper of Congo, and the rhinoceros-viper of Gabun; the European vipers, the most dangerous of which is certainly the asp of France, which is exceedingly numerous in certain regions.

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* CALMETTE: *Le Venin des Serpents*, Paris, 1896.

The effects of the bites of venomous serpents on man and animals are generally well known to the public; it is well to recall them, nevertheless. From the moment the bite has been inflicted, complete symptoms of poisoning develop, attended by a condition of extreme and increasing weakness, with vomiting, hemorrhage, and decomposition of the blood. There are, besides, particular effects which vary with every venom.

The following table by Calmette * gives the comparative toxicity of various venoms, taking as the standard of comparison the quantity sufficient to kill a rabbit in three or four hours:

Naja tripudians	0.00047
Naja hagé	0.0003–0.0007
Acanthophis antarctica	0.001
Ceraste	0.0017–0.0021
Haplocephalus variegatus	0.0025
Trigonocephalus	0.0025

Nature of Serpent-venoms. — These venoms are homogeneous liquids, somewhat more dense than water, in which they are soluble, slightly colored green or yellow, transparent, and insoluble in alcohol; they contain from 30 to 35 per cent. of solid matter. When fresh, they have a slightly acid reaction. Towards chemical reagents, and

* CALMETTE: *Annal. Instit. Pasteur*, VIII, p. 276; IX, p. 229.

particularly acids, they behave like albuminoids; almost all the combinations they afford with the various albuminoid reagents are active, despite their insolubility. According to Gautier, they are decomposed by caustic potash.

According to numerous researches, oxidizers like potassium permanganate, the hypochlorites, hydrogen peroxide, and gold chloride (in 1% solution) destroy the venoms; in certain cases when immediately injected hypodermically in the poisoned region, these substances are excellent antidotes *in vivo*.*

We shall not here enter upon a detailed study of the toxic albuminoid principles of serpent-venoms; moreover, our knowledge is rather vague, as it is, on a number of points. It will suffice us to know that, taken altogether, the active albuminoids of these venoms are numerous, and that each venom has its own particular active constituents, differing according to the species and variety of the snake.

Each one of these substances acts more or less rapidly, and may be associated with different principles which give rise to the variability of the action of these toxic agents. Among these toxic albuminoids, the most virulent appear to be true albumins and globulins, followed by the

* Winter and Blyth: *The Analyst*, 1877, p. 204; Lacerda: *Compt. rend. de l'Acad. des Sciences*, xciii, p. 466; Calmette: *Annal. Instit. Pasteur*, vi, p. 175, and viii, p. 278.

nucleo-albumins, as we have already stated; there are also found in venoms alkaloidal bases, but these principles are present only in very slight quantity. These bases are but very slightly toxic compared with the toxins that accompany them.

Natural Immunity towards Serpent-venoms.— Certain animals exhibit a natural immunity toward snake-bites; among them are the snakes themselves, the hog, the hedgehog, and the mongoos (an Egyptian rat); the blood of these animals contains apparently an antitoxin.*

Fontana † had remarked that snakes were quite unaffected by the bite of the viper, even when inoculated with the venom hypodermically. Physalix and Bertrand ‡ confirmed these statements, and showed that the snake perfectly resisted quantities of viper-venom capable of killing at least 20 guinea-pigs. According to these scientists, this natural immunity is due to the existence in the blood of toxic principles analogous to those of viper's venom—principles that exist in the labial glands of the snake, and pass into the blood and the fluids via the internal secretions. These writers, and also Calmette, have shown that the blood of venomous serpents becomes antitoxic when heated.

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* *Compt. rend. de l'Acad. des Sciences*, CXXI, p. 745; JACODOT: *Arch. de Médecine Navale*, VII, p. 390.

† *Traité sur le Venin de la Vipère*, Florence, 1781.

‡ *Archives de Physiologie*, 1894, p. 423.

It has been known for a long time that the hedgehog and the mongoos eat certain venomous reptiles, and eagerly hunt for the vipers in particular. When the hedgehog is bitten, which happens quite often despite its dexterity, it resists the viper-venom quite well. Physalix and Bertrand * have experimentally demonstrated that the hedgehog withstands a dose of viper-venom capable of killing at least 40 guinea-pigs. Levin † has shown that young individuals are less resistant, and it is concluded from this, and perhaps incorrectly so, that the immunity of the hedgehog is naturally acquired, rather than inherent. Bertrand and Physalix have nevertheless shown that on heating the blood of the hedgehog to 88° C. it manifests an antitoxic power toward serpent-venom *in vitro*.

Artificial Immunity toward Serpent-venom. — Immunity may be conferred upon every individual by utilizing the method of habituation. This fact was simultaneously elicited by Calmette, Bertrand, and Physalix. To effect the immunity these scientists prepare an antivenomous serum and inject it into animals, giving at first very small quantities of the diluted venom, and gradually increasing the doses, and the periods intervening

* *Bull. Muséum Histoire Naturelle*, 1, p. 294; *Compt. rend. Soc. de Biol.*, 1899, p. 77.

† *Deutsche med. Woch.*, 1898, p. 629.

between the injections. At the end of about two months of this treatment, the immunity has reached its maximum. Certain rabbits, thus slowly inoculated, have been able to withstand 0.04 Gm. of the venom of the naja at a single injection; such rabbits then yield a vaccinal serum.*

At the Institut Pasteur at Lille there is prepared in this manner an antivenomous serum from the horse; it is capable of acting upon 20 000 times its own weight. This has rendered great service in the treatment of snake-bites, particularly in hot countries, where the accidents are of daily occurrence. *In vitro* it acts quite as well preventively as therapeutically. It arrests the effects of the naja, the horned ceraste, the trigonocephalus, the rattlesnake, and of almost every one of the venomous serpents known.

The relatively considerable immunity possessed by certain snake-charmers, and which passes for a magical gift, is due to nothing else but a natural immunity, acquired perhaps by heredity, and it always appears to follow as a result of a non-fatal snake-bite.

Venoms of Batrachians and Saurians. — We observe here a fundamental difference between these poisons and those of snakes, as we shall

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* *Annal. de l'Instit. Pasteur*, 1895, p. 229; *Compt. rend. de l'Acad. des Sciences*, CXXII, p. 203.

see. These latter, in fact, appear to owe all their toxicity to true toxins which they contain, while the poisons of batrachians and saurians are chiefly composed of alkaloidal bases.*

The poison of toads and frogs (studied by Faust, Bertrand, and Physalix) is chiefly secreted by the glands of the subcutaneous tissues of these animals; it has but a very slight action on the unbroken skin, but it rapidly inflames the nasal and buccal conjunctival mucosa. The poison is a yellowish liquid, milky and viscid, with a waxy odor and an insupportably bitter taste. It is strongly acid and caustic. When dried, the poison yields to ether a fatty matter which, when absorbed by an animal, plunges the latter into a coma that may end in death.

The residue insoluble in ether contains the non-toxic albuminoids, and ptomaines, such as methyl-carbylamine,† and isocyanacetic acid, resulting from the decomposition of a lecithin that appears to be soluble in ether.

To obtain this venom, Physalix and Bertrand ‡ skin the toads, first chloroformed, and dry the skins in a vacuum over sulphuric acid; the skins are then cleaned by treating with carbon disulphide to remove fatty matters, and the toxic

* Cloez: *Compt. rend. de l'Acad. des Sciences*, xxxiv, p. 592.
† *Ibid.*, xcviii, p. 538.
‡ *Ibid.*, cxxviii, pp. 45–48.

principles removed by means of 95-per cent. alcohol; the poison so obtained, however, is impure. A better procedure is to express the parotid glands which have been placed in distilled water. Faust found in this venom a principle which he named *bufonin*. Physalix and Bertrand isolated from it also a resinoid substance soluble in alcohol and in a large excess of water; this substance, which they named *bufotaline*, acts upon the heart. These authors have also obtained another substance which has a paralyzing action, and which they have named *bufotenin*.

The poison of the common toad acts as a paralyzant upon the heart and on the spinal marrow *; that of the common frog possesses similar properties. The poison of the tritons is quite analogous to that of the toads; it contains a lecithin hydrolyzable by water with the formation of alanin, formic acid, and alpha-isocyanopropionic acid.

Zalnosky † isolated from the glands of the skin of the salamander a white, thick, bitter and alkaline liquid poison, containing a highly poisonous alkaloid, *salamandrine*, or *samandarine*, which acts on the brain, the medulla, and the spinal cord, and which has the formula $C_{54}H_{60}N_2O_5$; it is a strong base and yields crystallizable salts.

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* P. Bert: *Compt. rend. de la Soc. de Biologie*, 1885, p. 524.
† *Bull. Soc. Chim.* [2], VI, p. 344.

Fish-poisons.* — Very little accurate knowledge is extant regarding these. Many fish are poisonous, and among them are the synanceia, found in the Indian Ocean between the Netherland Isles and New Caledonia; considerable numbers are found in the neighborhood of the latter locality. These fish are provided with spiny rays which are in direct communication with a poisonous system having its seat in the dorsal fin. The prick of one of the spiny rays of this fish may under certain circumstances result fatally, and in every case it causes a rapid and painful gangrene.

From the reservoir the poison is conducted to the sharp extremity of the spines by a deep channel with which each spiny ray is provided; the animal has 26 poison-sacs, two for each ray, and the sacs burst when the corresponding sting is in any manner compressed.

The poison is an odorless liquid having a slight styptic or acidulous taste, and exhibiting a bluish fluorescence; it rapidly becomes turbid.

The weevers, which are numerous on the shores of the Mediterranean Sea, and which are also met with in the northeastern portion of the Atlantic Ocean, are likewise very dangerous, which explains their popular names "viper-weever," "spider-

* Bofford: *Thèse de doctorat en Médecine—Les Poissons venimeux*, Paris, 1889; O. Arcos: *Thèse de doctorat—Essais sur les accidents causés par les poissons venimeux*, Paris, 1887.

weever," etc. These fish are provided with a double set of poisonous apparatus, the one opercular, which is the more dangerous, and the other dorsal. The opercular spine has a double channel in connection with a conical cavity hollowed out in the base of the opercular bone. The bottom of this cavity is provided with special cells which secrete the poison. The dorsal glands have a similar structure.

The poison of the weever is a liquid, limpid when the fish is alive, and turbid when dead; it has a slight bluish fluorescence, is neutral in reaction, and is coagulated by acids and bases. It acts as a paralyzant, its action being exerted on the medulla and spinal cord; it retards the heart's action.

These examples will suffice; and we will not dilate further on this subject, because, as already stated, but little is accurately known regarding the subject, and what is known may be summed up as follows: Fish-poisons always give rise to an intense pain, frequently with motor paralysis, followed by paralysis of sensation; they affect the heart, arresting it in diastole; and they are more dangerous to fish and cold-blooded animals than to mammifers.

Poisons of the Hymenoptera.*—The poison system of the bee, and of such insects as the wasps, bumblebees, etc., is known to consist of a hollow

* PHILOUZE: Venin des Abeilles. *Annales de la Société Linn. du Maine-et-Loire*, IV.

sting consisting of two sharp needles communicating with two poison-bearing glands, and forming a flexible tube. One of these glands secretes an acid liquid (formic acid); the other secretes an alkaline fluid.

The action of the bee-poison is very often benign, but there have been cases where death followed the infliction of numerous stings.

Our information regarding the poison of the cantharides and flies is very vague *; the same is true of the poisons of various arachnids, acarides, and myriapoda. So far as spiders are concerned, it is known that their poison is an oily liquid having an acid and bitter taste, and containing a toxalbumin derived from the skin of the insect. The bite of the ordinary spider occasions simply a slight local pain, with redness; that of the large poisonous spider, however, may kill the larger animals, and even man.

Poison of Scorpions.†—This poison is a colorless, acid liquid, having a higher specific gravity than water, in which liquid it is soluble. The famed legend of the suicide of scorpions is well known to all. It is stated that when the insect finds itself in a position where its death is inevitable, it stings itself, and dies from the effects of its own poison.

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* Joyeux-Laffriée: *Thèse de doctorat en Médecine*, Paris, 1883; P. Bert: *Compt. rend. de la Soc. de Biol.*, II [4], p. 136.

† Calmette: *Annales de l'Instit. Pasteur*, X, p. 232.

A simple method has even been described of bringing this result about experimentally by surrounding the insect with a circle of fire. Bounne, of Madras,* who has studied the procedure, has demonstrated its entire falsity by showing, first of all, that the insect dies from the effects of the excessive heat, and further, that the poison of the scorpion is harmless to individuals of the species that furnish it.

Metchinkoff † has confirmed these facts, and has moreover demonstrated that the blood of the scorpion possesses an undoubted antitoxic power against the poison of the insect.

The poison of the scorpion serves it to kill the insects which are its prey. Frogs and birds stung by the scorpion also generally die. A dose of 0.0005 Gm. kills a guinea-pig in less than one hour; and according to Calmette ‡ less than 0.0005 will kill a white mouse in two hours. Oxidizers destroy the toxicity of the poison. Guinea-pigs immunized against the poison of the scorpion resist perfectly very large doses of the poison.

Poisonous Blood and Serums.—It is an almost general fact that the blood and blood serum of batrachians, eels, lampreys, snakes (even non-poisonous ones), and hedgehogs are very poisonous.

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* *Proceedings of the Royal Society*, XLII, p. 17.

† METCHNIKOFF: *L'Immunité*, p. 344.

‡ CALMETTE: *Annal. de l'Instit. Pasteur*, X, p. 232.

Mosso has found in the blood serum of the lamprey a toxin possessing a strong hemolytic power, and which he has named *ichthyotoxin*. 0.5 Cc. of this serum injected into a dog kills it in a few minutes. He also observed, in 1888, that the blood of the eel, in like dose, kills a dog almost immediately, and that the blood contains an ichthyotoxin analogous to that of the lamprey.

This substance, which appears to be closely allied to the sero-albumin of the blood, has a phosphorus-like, sharp, and burning taste. By digestion it loses its toxicity, as well as by heating at 68° to 70° C. It is easily obtained by precipitating with ammonium sulphate the serum of eels, and dialyzing the precipitate dissolved in water. The power of this substance is almost as great as that of the cobra poison, 0.002 Gm. being instantly fatal per kilo of dog.

The blood of snakes is likewise very toxic; the same is true of the blood of the viper, as 0.02 Cc. will kill a guinea-pig in two hours. All these bloods lose their toxicity when heated above 70° C. The serum of the hedgehog is peculiar in this respect; when heated at 38° C. for fifteen minutes it loses its toxicity, but it then possesses an immunizing power against the poisons.

The subject possesses great interest, because it was in studying these immunizing properties that

Camus and Gley,* and later on Kossel † and Tchistowitch,‡ discovered the first anticytotoxin,§ which they obtained by treating the animals with increasing quantities of the serum of eels. On mixing the antitoxic serum of these animals *in vitro* with the red blood-corpuscles of the species furnishing the serum and of the hemolytic serum of eels, it is found that the blood-corpuscles kept quite well.

As to the blood of the hedgehog, we have already seen that Physalix and Bertrand have shown that it may be a counter-poison towards serpent-venom under certain conditions. In its normal condition it is highly toxic.

Poisonous Meats.—It is particularly among the fish that we find these normally present, and it is

* *Archives internat. de Pharmacodynamie*, III and IV.

† *Berliner Klin. Wochenschr.*, 1895, No. 7.

‡ *Annal. de l'Instit. Pasteur*, XIII, p. 406.

§ The name "cytases" or "alexins" has been given to hemolyzing diastatic substances which are found in certain serums. It has been known for a long time that the serum of the blood of many animals destroys the red blood-corpuscles of other and different species. The chemical composition of these cytases or alexins is not yet definitely known, but the substances rank among the albuminoids; they are destroyed by a temperature of 55° to 56° C., and act only in saline solutions (Ehrlich and Morgenroth, *Berlin. Klin. Woch.*, pp. 6 and 481). The cytases or alexins, which will be studied in another volume of this collection, and which will discuss the active principles of the immunizing serums, constitute one of the numerous soluble intraleucocytary ferments, and they pass into the serous liquids of the organism only as the result of a rupture of or injury to the phagocytes.

a singular fact that, for a given species, the toxicity frequently depends upon the period of the year. Thus, at the period of spawning, certain fish may be extremely poisonous, or, on the contrary, may entirely cease to be so. The anchovy ballassa from the shores of India occasions death even in very small quantity; the poisonous meltite of the same seas causes violent vomiting; the fugu of the Japanese seas possesses an extreme poisonousness at the spawning period, while, on the contrary, it is perfectly innocuous at all other periods.

Numerous cases of poisoning have been chronicled every year by the journals, due to the ingestion of mussels; in the flesh of these crustaceæ is found a dangerous toxin, *methylotoxin*. The flesh of oysters is also unwholesome at the spawning period.

The toxic symptoms caused by these animals become apparent in not less than twenty-four hours after ingestion. The poisoning due to these fresh meats must not, however, be confounded with that caused by tainted or spoiled meats.

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